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FACTORS AFFECTING RECOVERY OF MOTOR FUNCTION AFTER NERVE LESIONS

BY

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(From the Department of Zoology and Comparative Anatomy, Oxford)

(RECEIVED 4TH JULY, 1942)

IN spite of the very great amount of material available from studies of nerve injuries in man we still have little thoroughly reliable information as to the factors which influence the degree of final recovery. Diagnosis, prognosis, and therapy of nerve lesions would be easier if there was less doubt about the variables which control the speed and degree of recovery. This paper reports the results of an attempt to define more exactly the influence on final recovery of (1) the nature of the lesion, (2) its level, (3) interference with blood supply of the limb, (4) age of the subject, (5) infection, and (6) delay of suture. Study of clinical material has failed in the past to provide answers to these questions mainly because the variables were so numerous. The cases generally have followed war wounds or accidents; the nerve has been injured over varying lengths; the blood supply has been damaged or there has been infection; surgical treatment has varied from case to case and many other factors have been involved which have made comparisons of clinical cases difficult or impossible. Experiments can avoid some of these uncertainties, but they must be arranged so that the criterion of recovery gives a real index that the nerve and muscle have returned to a useful functioning biological unit. Previous estimates of return of motor function in animals following injuries to limb nerves have been mostly restricted to observations of either the return of muscular contraction in response to electrical stimulation of the affected nerve, the so-called "indirect" electrical excitability, or of the restitution of normal use in the affected limb. The reports of the return of indirect excitability may be of two kinds: (*a*) statements that electrical excitability was present after a certain time (Kilvington, 1908), or (*b*) a series of observations made at different times, the earliest positive observation indicating roughly the time of onset of this type of recovery (Holobut and Jalowy (1936), Howell and Huber (1892), Bentley and Hill (1936)). Of these two types of report the second is obviously the more valuable from a comparative point of view. But reports of the first type are often of considerable value, since they indicate the presence of regenerated fibres, both in the nerve trunk and in the paralysed muscles, and that the muscle endings formed are such that electrical stimulation of fibres in the nerve is adequate to bring the muscle to contraction. But such observations do not imply that a recovery of reflex or voluntary movement has necessarily taken place. Certain processes have to take place in a nerve before it becomes "functionally complete," and these processes may not be over even though many of its fibres have made connections with the periphery, and the muscle responds when the nerve is stimulated electrically (Gutmann *et al.* (1942)). Thus it is possible for a return of indirect electrical excitability to take place without any return of motor function. Clinically, the important entity is the voluntary or reflex movement. Observations alleging "functional recovery" in animals based upon a return of indirect excitability in the absence of evidence of return of voluntary movement have a limited value only. Most observations on the return of voluntary movement take the form of a statement to the effect that the gait of the affected limb eventually became normal. Such observations have been recorded after using nerve grafts (Ingebrigsten (1916), Nageotte (1922)) as a test for the effect of electrotherapy (Friedländer (1896), Chor *et al.* (1939)) and of nerve crossing (Howell and Huber (1892), Osborn and Kilvington (1911), Kennedy (1913), and Barron (1934)). The main defect of observations on gait is that they take no account of the recovery of voluntary movements in individual muscles innervated by the operated nerve, and thus it is not possible to estimate at all accurately the time of onset of recovery in these muscles. At most one may roughly estimate the time of the appearance of a generalized co-ordinated movement. Moreover, a considerable degree of inco-ordination of movement is apparent in the first voluntary movements of reinnervated muscles, as a

result of the heteroinnervation of muscle endings. This is especially noticeable after nerve crossing (Barron (1934), Sperry (1941)), but it may occur to a certain extent following division and suture of a nerve (Watrous and Olmsted (1941)).

Both in man and other mammals it is possible that this inco-ordination may be partly overcome by a process of readjustment in the centres concerned (Watrous and Olmsted (1941)). But this readjustment takes place in the period immediately following the incidence of motor recovery. Therefore observations on gait dating the onset of recovery as the time of commencement of co-ordinated movement will be overestimates, for such times include both the actual time of recovery and the time required for " relearning." In addition, many synergic groups of muscles collaborate in walking movements, and may give an appearance of recovered function in cases where recovery has in fact not taken place. Thus improvement or recovery of function has been recorded at a time when no regenerating fibres could possibly have arrived at the muscle (Friedländer, 1896). Observations on the recovery of gait are therefore not conclusive or exact tests of the recovery of voluntary movement. A more reliable estimate of the time of onset and progress of recovery of voluntary movement following nerve repair in animals may be made by restricting observations to the function of a small group of muscles known to be innervated by the nerve whose recovery is being followed, and whose action cannot be imitated by any other set of muscles (for example Bender and Fulton (1939), after section of the oculomotorius nerve in Macacus). In this way onset of recovery may be accurately dated, and errors due to trick movement avoided. The difficulty is to find a movement which meets these conditions, which may be easily elicited and which may allow frequent examination of the animals essential for the study of onset of recovery.

In order to test factors influencing the recovery of motor function, and to follow the different stages of the process of recovery, it is first necessary to use a standard method of interrupting the nerve. Such methods as cutting the nerve without suturing (Holobut and Jalowy (1936), Friedländer (1896)), injecting the nerve with alcohol (Wolf, 1940), and sutures à distance (Vanlair, 1894) introduce great variations. Even simple stitch sutures cannot all be made alike. Thus Chor *et al.* (1939) observed onset of recovery after stitching the sciatic nerve at times varying between 55–158 days. Such variations made comparison difficult; for instance, Perroncito (1908), when comparing the constant results obtained from anatomical data with the " immense contraindications and variations of the physiological experiment " stated that " questions of anatomical regeneration of nerves and of functional healing although connected have to be considered separately."

The method of crushing a nerve offers the minimum variation in the time of onset of recovery, and may be thus used with advantage when factors influencing the progress of recovery are being studied. Lee (1929) has maintained that crushing is an uncertain procedure of interrupting a nerve, but if properly done it is followed by complete degeneration of all the fibres. The constancy of the results obtained by crushing permits better assessment than by any other method of trauma.

Methods

Movements which may be elicited reflexly have been chosen as tests indicating onset of recovery of motor function. Postural reflexes have been found to be especially useful. In most of the experiments to be described observations have been made mainly on a small group of muscles innervated by the peroneal nerve of the rabbit, the function of which is to spread three of the toes of the hind limb. These muscles may be caused to contract reflexly as first observed by Langley (1915) in cats, by holding the animal by the loose skin of the back and then suddenly lowering it. The muscles involved in this reflex are the small peroneals (Mm. peronei II, III, IV) innervated by the peroneal nerve, and the M. abductor hallucis innervated by the tibial nerve.* The peroneal muscles spread the second, third, and fourth toes, while abduction of the first toe is a function of the M. abductor hallucis. Reflex spreading of the 2nd, 3rd, and 4th toes thus constitutes an index of peroneal nerve function, while reflex abduction of the first toe characterizes tibial nerve function. Following section of the peroneal nerve there is a loss of ability to spread the 2nd, 3rd, and 4th toes which cannot be simulated by a " trick " movement. During regeneration of the peroneal nerve the first response is a mere flicker of the 4th toe; the spreading increases in amount from day to day, gradually involving the 2nd and 3rd toes. By the use of an arbitrary scale, which may be called the " spreading index," it has been possible to make a rough estimate of the state of recovered function. Degrees of spreading have been indicated as follows: *degree* 1, just visible spreading of the 4th toe alone, sometimes also of the 2nd and 3rd toes; *degree* 2, slight spreading of all toes; *degree* 3, spreading of all three toes, but less than elicitable in the normal animal; *degree* 4, full spreading of all three toes equal to normal as determined before operation or by comparison with the opposite and control side. By means of daily examinations the progress of recovery in a single case, and the difference in the final degree of recovery attained after different procedures may be estimated. Note has also been made of the progress of recovery of the other muscles innervated by the peroneal nerve, so as to allow comparisons between the recovery of muscles with nerves of different lengths. Other criteria of muscle recovery have been examined, namely (1) the indirect excitability or response to electrical stimulation of the nerve either (*a*) through the skin, or (*b*) after exposure of the nerve; (2) the direct excitability of the muscle; (3) the circumference of the limb in the region of the denervated muscles; (4) the weight of the muscles; (5) the disappearance of fibrillation.

The animals used have been rabbits of various ages and races, including some of a month old, which have given evidence about the effect of age on recovery rate. The nerve lesions have been made by aseptic operation under nembutal-ether anæsthesia when the nerve has been interrupted by one of four ways: (1) by repeated crushing at a single point by a fine smooth-tipped watchmaker's forceps; (2) by severance with scissors followed by suture with cockerel plasma (Young and Medawar, 1940); (3) by severance with scissors followed by suture with fine white silk stitches; or (4) by repeated crushing with forceps over a considerable length (4 cm.).

* The name given to this muscle by Krause (1884) and in other text-books on the anatomy of the rabbit (Bensley (1938)) is M. extensor hallucis. As the main function elicitable reflexly is one of abduction rather than extension, the muscle might be more appropriately named M. abductor hallucis.

The Recovery of Motor Function after Lesions of the Peroneal Nerve

Functions of the peroneal nerve

Most of the following studies depend on knowledge of the sequence of events during recovery of the peroneal nerve. We will therefore first describe the stages of recovery after interruption by crushing at a single point of the continuity of the axons of that nerve. The muscles innervated by the peroneal nerve and their functions (elicited by stimulation of the nerve) are:

M. tibialis anterior: dorsal flexion and some supination of the foot.

M. extensor digitorum: dorsal flexion of the toes.

M. peroneous longus (or primus): pronation and some plantarflexion of the foot.

M. peroneus secundus: abduction of the 4th toe and some abduction of the other toes.

M. peroneus tertius: dorsal flexion of the 3rd toe and some abduction of the 2nd and 3rd toes.

M. peroneus quartus: plantar flexion and some abduction of the 2nd and 3rd toes.

Thus the functions of the muscles innervated by the peroneal nerve are dorsal flexion of the toes and the foot, pronation of the foot and abduction (spreading) of the 2nd, 3rd, and 4th toes.

Recovery after Crushing of the Peroneal Nerve

The palsy after interruption of the peroneal nerve is characterized by dropfoot and the absence of the spreading reflex (Fig. 1). These features do not produce any marked influence on the stance and gait, which appears normal except for some abduction of the foot when sitting and some dragging of the foot when hopping. In some cases the toes are kept in marked plantar flexion and the animal walks on the dorsum of the toes, where sores may develop. These cases are rare and observations of the gait alone do not allow estimates of the onset of recovery. The dropfoot is marked immediately after interruption of the nerve, but becomes less or disappears, often long before reinnervation of the muscles. This is due to the sitting posture of the animal, which fixes the foot in a bent position. In Man, on the other hand, where the opposite condition obtains, the dropfoot continually increases. On account of this fixation it is not easy to determine the time at which dropfoot recovers in the rabbit. The movement of dorsal flexion of the foot may be elicited reflexly as a nociceptive reaction by pricking the sole. This reflex, however, is not very suitable for a study of recovery because being a general shortening reaction it involves movements of muscles of the hip which may produce actions similar to those of the muscles paralysed by the peroneal nerve lesion. It is easier to produce dorsiflexion of the foot by gentle lowering of the animal in the upside down position.

FIG. 1.—Palsy after interruption of the peroneal nerve, characterized by dropfoot and absence of the spreading reflex.

Of the functions mediated by the peroneal nerve the spreading (abduction) of the 2nd, 3rd, and 4th toes may be most easily studied. Even at rest the effect of interruption of the nerve is clearly seen in the close apposition of the toes, producing a narrow foot (Fig. 1). With the nerve interrupted at the level of the knee by a crush the spreading reflex reappears after 23 to 27 days (12 animals), the earliest sign being a movement of the 4th toe. For the first 2 or 3 days this is a mere flicker, inconstant and sometimes disappearing on repetitions. This is the condition characterized as degree 1. Two or 3 days after the reappearance of the abduction of the 4th toe the spreading of the 3rd and 2nd toes appears (degree 2). During the subsequent days the amplitude of the movement increases (degree 3), finally to return to normal (degree 4) at an average of 8 days (Fig. 2). In some animals the extent of abduction continues to increase, becoming greater than that normally found. This has been observed

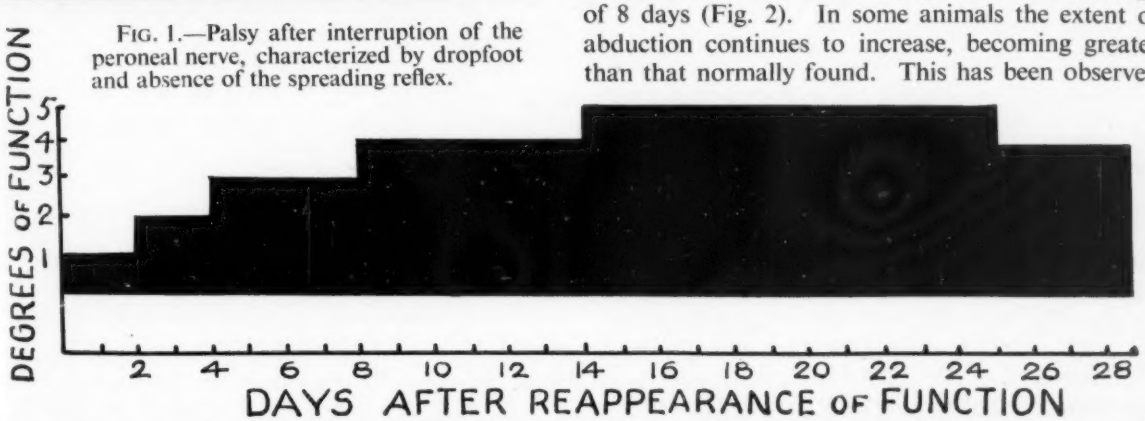

FIG. 2.—Course of recovery of the " spreading reflex " in a typical case after crushing the peroneal nerve at the knee (20 mm. above entry to the M. peroneus longus). The ordinates show degree of spreading observed. For the period from 14 to 25 days after appearance of the spreading it is greater than that normally observed.

in 6 animals, in which a control side had been left for comparison. This over-functioning, which may be expressed as degree 5, is only a temporary phenomenon, and after reaching a maximum about 1 to 3 weeks after the onset of recovery subsequently declines until the movement is of normal extent (see Fig. 2). This over-functioning may be due to the excessive early innervation (Boeke, 1916), and its later correction may indicate that the initial number of fibres is later reduced.

As explained above, it is difficult to determine the exact amount of recovery of the other muscles supplied by the peroneal nerve. Dorsiflexion of the foot usually appears about one week after the first appearance of spreading. It increases in strength in the next few days and becomes normal after about 1 to 2 weeks.

Recovery of Indirect Excitability

For some time before reflex functioning returns the muscles will contract when the nerve is stimulated with a faradic current. The time of onset of this indirect excitability has been investigated in a series of animals in which the peroneal nerve has been crushed at the knee. Fig. 3 shows the results from 36 animals in which the peroneal nerve has been crushed at the level of the knee and then exposed for faradic stimulation with bipolar electrodes a number of days before recovery had been expected. In addition the figure shows the times at which recovery of the functions of spreading and dorsal flexion have been seen after such lesions. The muscles begin to respond in the order of their distances from the lesion, the order being the M. peroneus longus, M. peroneus secundus, M. peroneus quartus, M. peroneus tertius, and finally M. tibialis anterior and M. extensor digitorum. The time between first appearance of indirect excitability and reflex function is about 5 days in the case of the M. peroneus secundus; this interval is nearly the same for the other muscles, whose function cannot be so exactly determined. When indirect excitability of a given muscle first reappears the threshold is unduly high, even above the lesion, presumably because of the need for a greater voltage to stimulate the few fibres which have become reconnected. Subsequently the threshold falls. Therefore, after all muscles have just recovered, by slowly moving in the secondary induction coil successive contractions of the muscles according to their distances from the lesion may be obtained. About 3 weeks later all muscles respond at the same threshold. Contraction of the muscles by stimulation of the nerve through the skin appears late, about a week after the first appearance of the spreading reflex. The most suitable point for stimulation is just below the knee, where the nerve lies very superficially. The same sequence of recovery as during stimulation of the exposed nerve is obtainable.

Measurements of Circumference

A further method of demonstrating changes during the process of regeneration in the muscles is the measurement of the circumference of the leg. At a point 15 mm. below the crista tibiæ the circumference of the leg has been measured with a thread at weekly intervals after the interruption of the nerve. Each measurement has been repeated three times and the mean taken. Even this somewhat crude method has proved sensitive enough to show

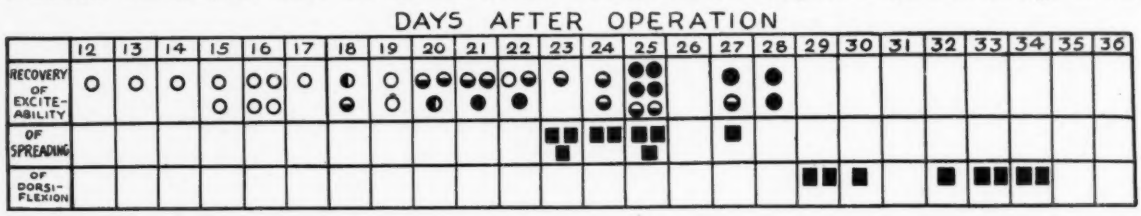
DAYS AFTER OPERATION
12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
RECOVERY OF EXCITE-ABILITY
OF SPREADING
OF DORSI-FLEXION

FIG. 3.—Onset of excitability and recovery of function after crushing the peroneal nerve about 20 mm. from the M. peroneus longus. Each circle represents an experiment in which the nerve was stimulated at a given interval after crushing. ○ indicates no muscles responding, ◐ response in m. peroneus longus, ◒ in m. peroneus longus and secundus, ● in all muscles innervated by the nerve.

Each black square shows the day on which recovery of spreading (second line) or dorsiflection (bottom line) was observed in one case. Thus the spreading reappeared between 23rd and 27th day.

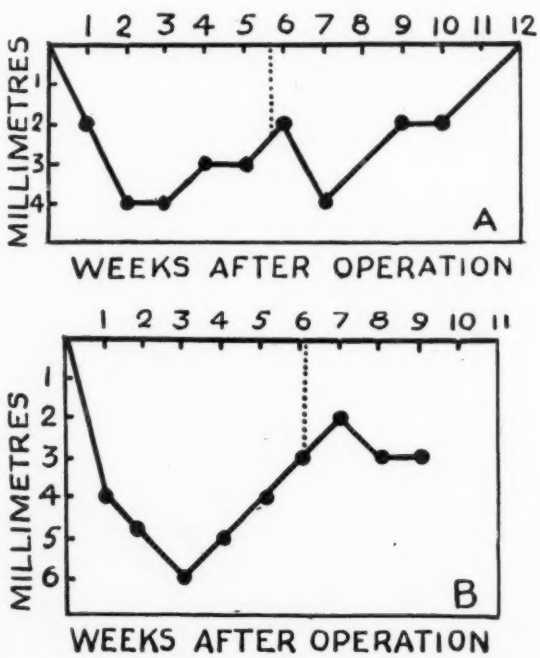

FIG. 4.—Differences shown by successive measurements of the circumference of the leg made 15 mm. below the Crista tibiæ in two animals in which the peroneal nerve had been crushed 80 mm. from the M. peron. long. The dotted line indicates the day of onset of the first appearance of reflex functioning.

the onset of the process of recovery. After interruption of the peroneal nerve the circumference decreases, and this decrease stops before either indirect excitability or reflex movements return (Figs. 4 and 5). In some cases it is found by calculation that the cessation of the decrease of circumference coincides roughly with the time at which regenerating fibres arrive at the muscle. The values from individual animals do not always give a smooth curve as that given by the average of the changes of circumference shown in Fig. 5, there being a margin of experimental error of 2 mm. at individual observations. When no regeneration occurs the circumference continues to decrease, though at a slower rate. In a case where a graft had been made (Gutmann and Sanders, 1942) the failure to show a regular increase in circumference had raised the suspicion that no union had been made. Necropsy confirmed that this has been the case.

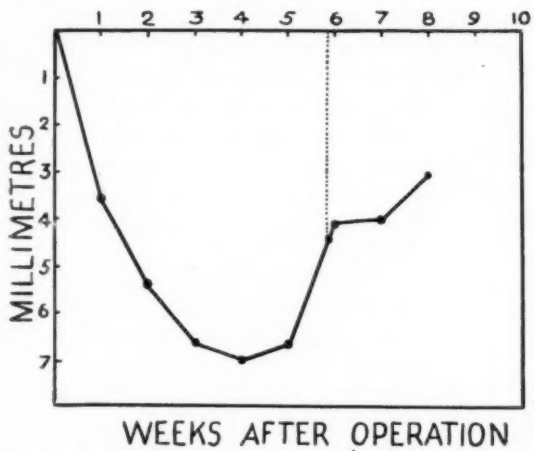

FIG. 5.—Average of the changes in circumference of the leg after crushing the peroneal nerve, calculated from 12 cases. The dotted line indicates the average time of first appearance of reflex functioning in these cases.

Electrical Excitability of the Muscles

Faradic stimulation of the muscle, either directly on the exposed muscle or through the skin, has always produced a response, even 8 months after denervation. Observations have been made on the threshold necessary for eliciting visible function (pronation, abduction of the 4th toe and dorsiflexion of the foot), and for the visible contraction of the muscles. After interruption of the nerve the threshold declines for 2 to 3 days and then increases. During the process of regeneration the thresholds fall again before onset of functional recovery. Some weeks after recovery following crushing of the nerve thresholds lower than that before operation have been observed in a few cases. The changes in threshold, however, are not great, and in view of the considerable strength of stimulus necessary to excite the muscles little reliance is to be placed on this method.

Cessation of Fibrillation

Fibrillations may be readily seen by light reflected from the surface of the muscles. Fibrillation does not cease with the return of indirect excitability or reflex function. About 1 week after return of the spreading reflex, when dorsiflexion is returning, fibrillations may be seen in all muscles, most prominently in M. extensor digitorum and in M. tibialis anterior. Two weeks after the appearance of spreading, fibrillation disappears from the peronei but may persist for 2 weeks in the two more distal muscles. Presumably, therefore, fibrillation only ceases in a given muscle fibre when it becomes innervated, a process which occurs progressively throughout each muscle.

Observations on the Weight of the Muscles

The peroneal nerve has been crushed on one side either, in one series, just before its entry into the M. peroneus longus, or, in another series, high up in the thigh about 110 mm. from the muscle. Necropsy has then been performed either at the moment of recovery of spreading, or, in other animals, at intervals of 1, 2, 3, 4, 6, and 12 weeks after recovery. The M. extensor digitorum and M. tibialis anterior have been excised and weighed. The muscles removed from the living animal have been placed in a Petri-dish on Ringer-soaked gauze and weighed after blotting twice with filter paper. Fig. 6 shows the percentage of the weights of the

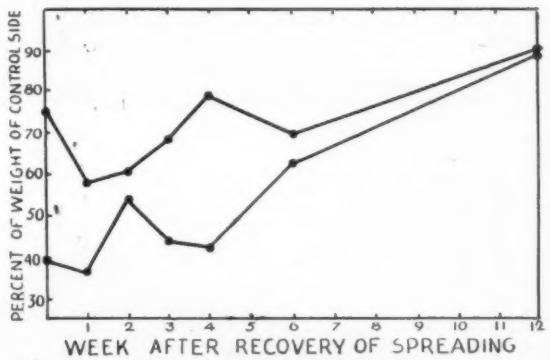

FIG. 6.—Diagram in which the percentage of the weights of the reinnervated M. tibialis ant. compared with the normal muscles of the control side were plotted against time after recovery, upper line after low lesions, lower line after high lesions.

reinnervated muscles compared with those of the muscles of the control side. It may be seen that even after recovery of spreading the atrophy is marked. This is to be expected as at this time the reinnervation of the muscles is not complete. Thereafter the muscles gain in weight slowly, but even 12 weeks after recovery of spreading the initial weight is not completely regained. At this time the initial difference in weight between high and low crushes due to the longer time of denervation ceases to be evident.

Summary of the Process of Recovery

By comparing a number of aspects of recovery after standard lesions at a standard distance a clear picture is obtained of the sequence of events. When the lesion is a crush made 20 mm. from a muscle, say the M. peroneus II, new axons arrive in the muscle 10 days after injury (Gutmann *et al.*, 1942). Soon after this the direct excitability of the muscles ceases to fall, while at the same time the circumference begins to increase, and the first muscle fibres begin to respond on nerve stimulation. The weight of the muscles increases slowly and is nearly normal 12 weeks after recovery. The first sign of reflex functioning appears some 5 days after onset of indirect excitability, and the power of the muscle continues to increase until it reaches normal about a week after the first reflex contractions, though it may become supernormal for a short time. The increasing extent of the movement during the days after its first appearance is presumably a result of increasing numbers of muscle fibres which become innervated.

Factors Influencing the Recovery of Function

Effect of Level of Lesion.—The process of recovery has been watched after crushing the peroneal nerve (*a*) high in the thigh—5 cases, (*b*) at the middle of the thigh—7 cases, and (*c*) just above its entry into the muscles—7 cases. The distances of the lesions from the entry to M. peroneus II are about 105, 40, and 20 mm. The progress of increase in the spreading reflex has been examined carefully in each case. By taking the average of the degree of spreading shown by all the animals of each set at each day after the beginning of recovery a clear picture of the process of recovery may be obtained (Fig. 7). It will be seen that the recovery of spreading is distinctly slower with the lesions more distant from the muscles, the complete recovery (degree 4) being reached at an average of 8 days in Group A, 8·4 days in Group B, and 13·5 days in Group C, after the beginning of recovery. It seems that the time between arrival of fibres at the muscle and onset of indirect excitability and recovery of function is longer after high than low crushes. The first fibres arrive in low lesions (20 mm. from the muscle) after 10 days, in lesions of the middle of the thigh (48 mm. from the muscle) after 16 days, and in high lesions (100 mm. from the muscle) after 27 days (Gutmann *et al.*, 1942). Indirect excitability returns in low lesions in 18 days, in lesions in the middle of the thigh in 30 days and in high lesions in 43 days after operation. Thus the difference between the time of arrival of fibres and the time of onset of indirect excitability is about 8 days after low, 14 days after middle, and 16 days after high thigh lesions.

When interpreting this difference it is to be remembered that after the more distant lesions the muscles have reached a greater degree of atrophy (see Fig. 6), which may be the reason for the later and slower recovery. It is probable, however, that a further reason is the more scattered arrival of fibres on account of the greater distance. Again, a greater degree of maturation may be necessary to achieve function over the greater length of regenerated nerve (Gutmann *et al.*, 1942). The relatively later recovery of longer stretches of nerve can be clearly tested by examining the times of recovery in cases in which the only variable is distance. To do this experimentally it would be

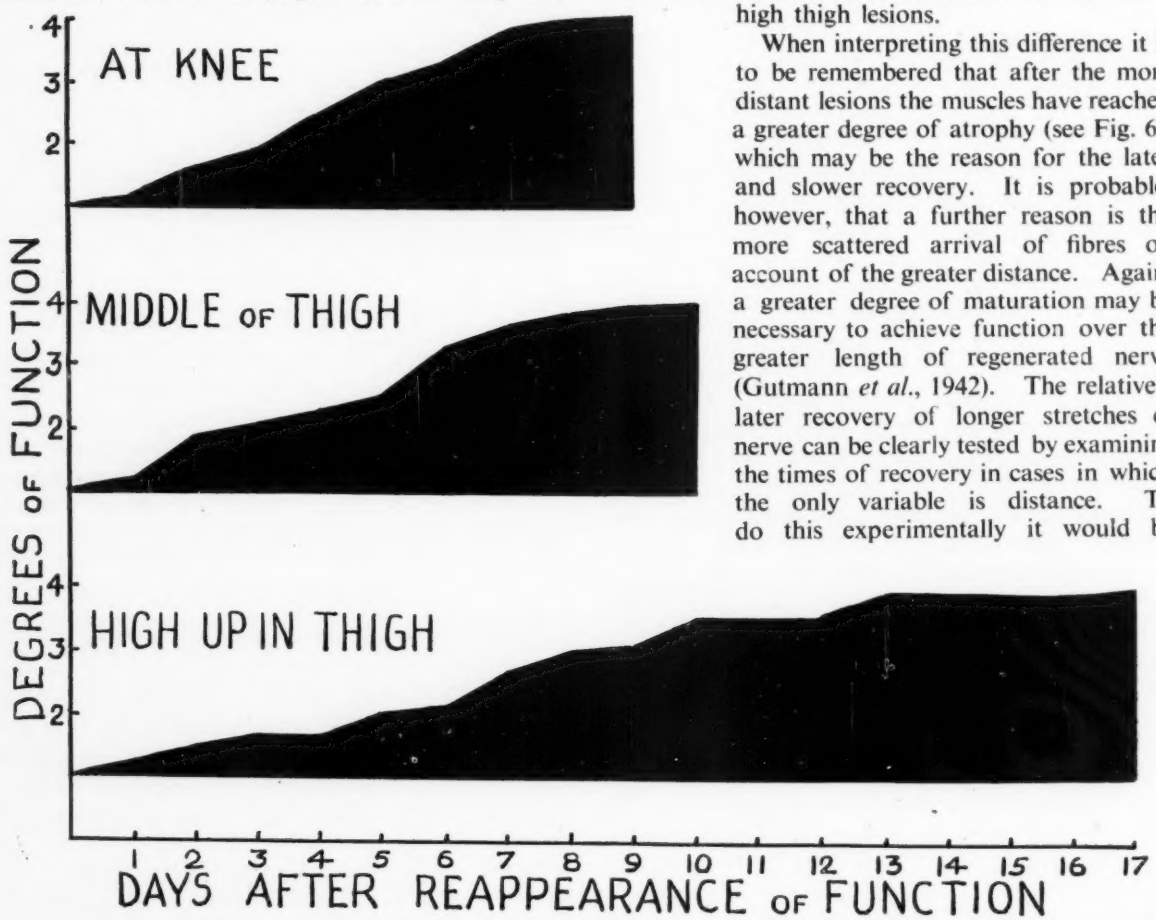
AT KNEE
MIDDLE OF THIGH
HIGH UP IN THIGH
DEGREES OF FUNCTION
2
3
4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
DAYS AFTER REAPPEARANCE OF FUNCTION

FIG. 7.—Rate of increase in degree of spreading during recovery after crushing the peroneal nerve at the levels shown. The average degree of spreading has been calculated at each day after its beginning by dividing the total " degrees of spreading " at that day by the number of animals.

necessary to compensate for the greater degree of atrophy imposed by the more distant lesions. This has not been attempted in the present series. Fig. 8

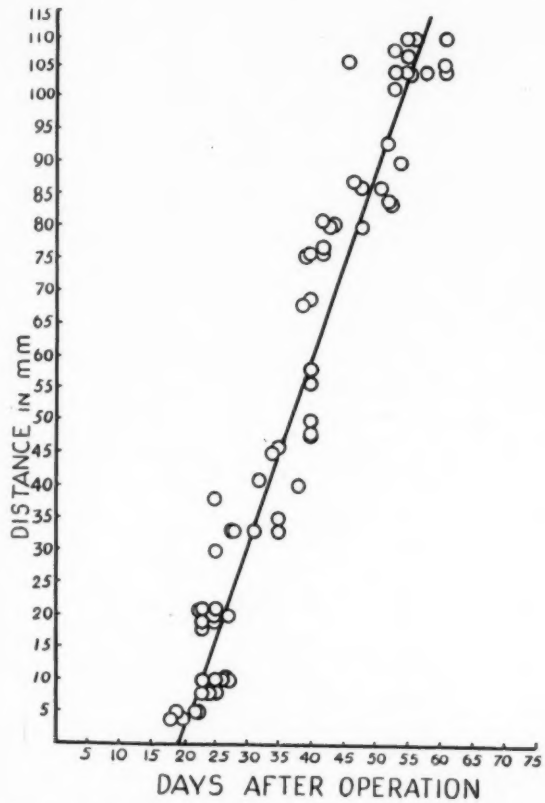

FIG. 8.—Graph showing times of recovery plotted against level of the lesions after crushing the peroneal nerve at varying distances from the M. peroneus longus. The line is the regression line, arithmetically calculated.

is a chart of time of first recovery plotted against the distance of lesion in 69 cases, including those already discussed by Gutmann *et al.* (1942), and 31 others. From these data the rate of advance of regeneration to a level of functional completion sufficient to enable spreading to be performed is given as $2{\cdot}77 \pm 0{\cdot}09$ mm./day. The latent period before functional completion begins to advance beyond the lesion is 18·2 days. These figures, since they include further data, are to be preferred to those already given by Gutmann *et al.* (1942), from which they show no statistically significant differences.

The point to be emphasized is that these points lie remarkably close to a straight line. If recovery of the nerve be relatively more slow in the distant lesions there would be a falling off in the upper part of the curve. The absence of any sign of this shows convincingly that with the distances and functions here considered the rate of recovery of the nerve is nearly constant. We conclude, therefore, that over the distance here considered the level of the lesion has no effect on the rate of nervous regeneration. The improvement after first appearance of recovery is, however, slower with the more distant lesions, probably partly because of greater atrophy and partly through the greater scatter in time of arrival of functionally complete fibres.

Effect of Type of Injury on Recovery

Recovery after severance and suture.—We may now compare the progress of recovery after severance and suture with that which has been described after crushing the nerve. Fig. 9 shows the times of first recovery observed after lesions at the various levels, including the figures quoted by Gutmann *et al.* (1942) and 8 others. From these results the rate of advance of functionally completed fibres is given as $1{\cdot}69 \pm 0{\cdot}34$ and the latent period before fibres are complete close to the junction as 27·7 days. The times of recovery are more variable than after crushing and the value of the estimate of rate is correspondingly reduced. The figure given is lower (though not significantly) than that given previously (Gutmann *et al.* (1942)) and considerably lower than the 2·6 mm./day obtained by considering paired data of high and low sutures in the same animal. The points shown in Fig. 9 include

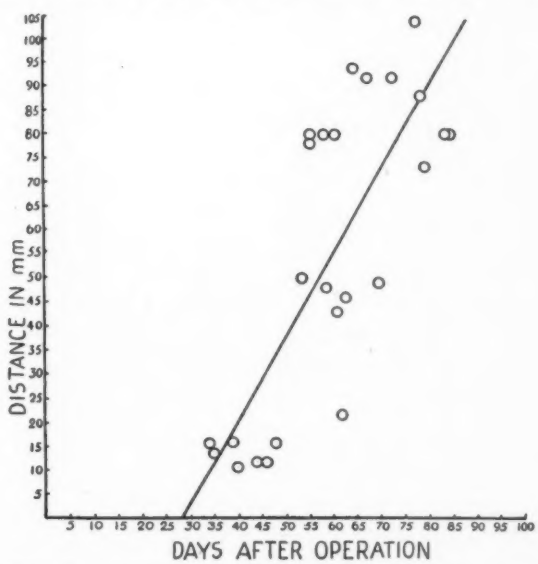

FIG. 9.—Graph showing times of recovery plotted against level of the lesion after suturing the peroneal nerve at varying distances from the M. peroneus longus.

some in which recovery has been much delayed; in these cases histological examination has shown that poor junctions have been made. These points tend to make the estimate appear low, but they are included here to show the full extent of the variability.

The increase in degree of spreading after its first appearance proceeds much more slowly than after crushing the nerve. Although some of the animals have been observed for as long as a year after suture, in no case has full recovery of spreading ever occurred. Fig. 10 shows a typical case of the progress of recovery and should be compared with Fig. 2. Fig. 11 is a photograph of an animal 110 days after operations in which the peroneal nerve has been crushed on the right and sutured on the left sides. The phenomenon of slower improvement

of function during recovery after high lesions is the same in sutured as in crushed nerves, but is less clear on account of individual variations.

The recovery of indirect excitability has also been

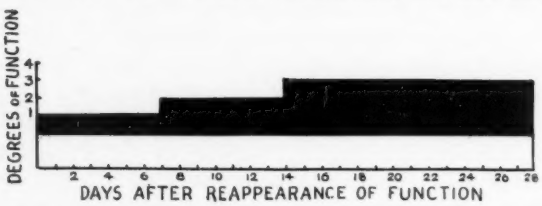

FIG. 10.—Course of recovery of the "spreading reflex" in a typical case after suturing the peroneal nerve 80 mm. from the M. peroneus longus. Compare Fig. 2.

tested in a series of animals by examinations a number of days before expected recovery (Fig. 12). As with crushed nerves, indirect excitability recovers before reflex function, the interval being some

FIG. 11.—Recovery of the spreading reflex 110 days after operation in a case in which the peroneal nerve has been crushed on the right and sutured with plasma on the left side at the same level. Notice the greater extent of spreading of toes on the right side.

10 days. Thus in animal 574 good sutures having been made in both peroneal nerves, 46 days later at a second aseptic operation on the left side there was no response on faradic stimulation of the nerve. Fifty-one days after suture the right side was examined and contraction obtained in the M. peroneus longus. Recovery of reflex function was seen on the 59th day on the left side and on the 63rd day on the right side.

Data obtained from the onset of indirect excitability suggest that a longer time elapses between arrival of fibres and onset of indirect excitability after suturing than after crushing. Fibres arrive at the muscle 21 days after sutures in the middle of the thigh (48 mm. from the muscle) and the onset of indirect excitability is observed about 47 days after operation. Thus the difference between the time of arrival of fibres and onset of indirect excitability is 26 days after sutures compared with 14 days after crushing at this level.

Measurements of circumference have been taken in the same manner as in crushed cases. These show the same general results, but are more variable. The initial values of circumference are obtained at a later time or not at all. Fig. 13 shows the curve

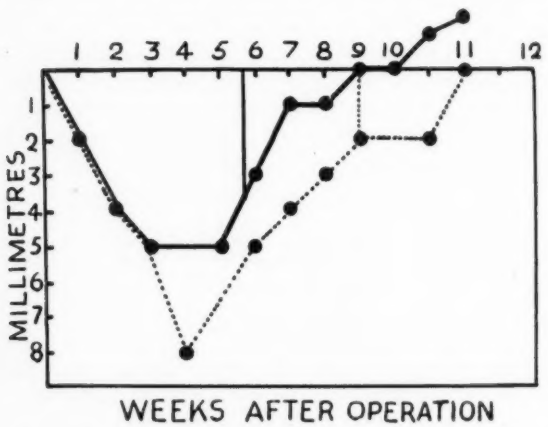

FIG. 13.—Successive measurements of the circumference of the leg made 15 mm. below the Crista tibiæ in a case in which the peroneal nerve has been crushed (continuous line) on the right side and sutured (dotted line) on the left side 48 mm. from the M. peroneus longus. The vertical lines indicate recovery of spreading.

of the values of circumference in an animal in which the peroneal nerve has been crushed on one and sutured on the other side at the level of the middle of the thigh. Fig. 14 shows the changes in threshold on direct stimulation of the M. tibialis anterior through the skin of the same animal.

Examination of the weights of the muscles in a few cases after suture has shown that, as after crushing, there is an initial difference between the

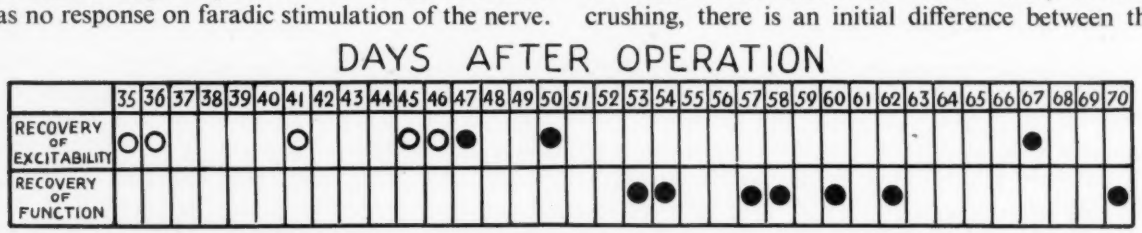

FIG. 12.—Onset of excitability and recovery of spreading after suturing the peroneal nerve 48 mm. from the M. peroneus longus. Each circle represents an experiment in which the nerve has been stimulated at a given interval after suture. ○ indicates no muscle responding, ● response in M. peroneus longus (first line) or recovery of spreading (second line).

weights when the nerve is sutured high and low. These differences eventually disappear, but the process after suturing seems to take longer. Thus in 3 animals in which the peroneal nerve has been sutured high on one side and low on the other the weights in grammes are:

	Suture low	*Suture high*
90 days after operation ..	2·28	1·56
192 „ „ ..	1·42	0·98
364 „ „ ..	3·20	3·13

After crushing the peroneal nerve the weights 90 days after operation are 1·96 gm. on the side with the low and 1·66 gm. on the side with the high lesions.

After suture, therefore, all processes of recovery are slower than after crushing the nerve. There is a longer delay before functionally complete fibres begin to advance down the nerve and their progress is more slow. There is also a longer delay between

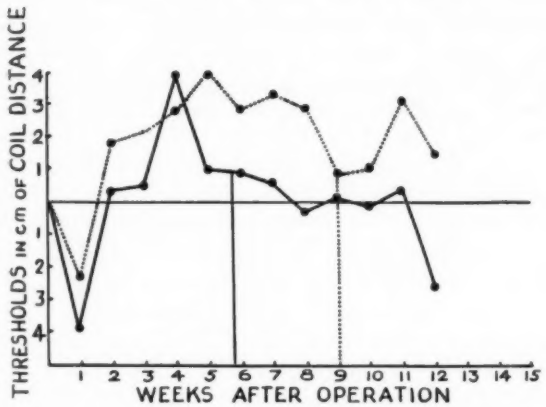

FIG. 14.—Difference in the direct excitability of the M. tibialis ant. stimulated through the skin in a case in which the peroneal nerve has been crushed on the right side (continuous line) and sutured on the left side (dotted line) 48 mm. from the M. peroneus longus.

arrival of fibres and indirect excitability, and a longer delay between appearance of indirect excitability and reflex function; finally the degree of the latter also increases more slowly. Some of these differences may be due actually to a slower advance of the processes of regeneration after sutures than after crushing. In crossing a suture line fibres are supported only by Schwann cells which have grown out with them, or to meet them; the condition of the fibres in this region may affect their advance and increase in diameter in the peripheral stump. However, a considerable part of the differences must be due to the smaller number of fibres reaching each level at a given time. A further factor influencing the final degree of recovery is probably the shunting of fibres into wrong channels, an event more probable after suturing than after crushing. It would be very interesting to be able to estimate separately the influence of these factors, but there are as yet no means of doing this.

No special series of animals has been operated on to estimate recovery after cutting and suturing with stitches. Suture with fine white silk has been performed in 3 animals and recovery of spreading observed after time intervals similar to those after union with plasma.

Recovery after crossing a nerve gap.—All the above tendencies are still further accentuated in the processes of recovery when this occurs in the presence of a gap between central and peripheral stumps. Gutmann and Sanders (1943) have reported recovery in one case out of 6 animals in which a gap of 2 cm. has been left in the peroneal nerve; it began only after 117 days and had advanced only to degree 2 after 160 days.

Recovery after crushing a length of nerve.—In 3 animals the peroneal nerve in the thigh has been crushed with large flat forceps over a length of 4 cm., a single narrow crush being performed on the other side at the same level to act as a control. The onset of recovery has been recorded at 61, 56, and 54 days on the side with the long crush and

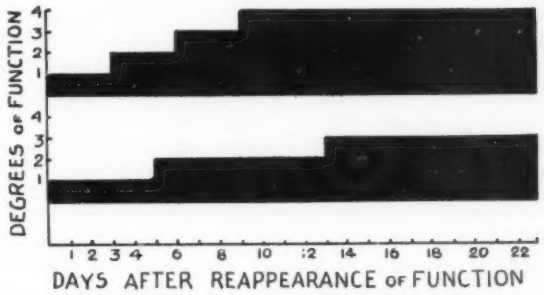

FIG. 15.—Course of recovery of the spreading reflex in a case in which the peroneal nerve was crushed at a single point (upper diagram) on the right side and crushed over a length of 4 cm. (lower diagram) on the left side.

compared with the control side at 51, 48, and 47 days. The degree of spreading has increased at a much slower rate in the nerves with the extensive crushes (Fig. 15), but has varied in the 3 animals. In one animal this difference was still manifest 200 days after operation. At necropsy no difference has been found between the muscle weights of the two sides, these being 3·21 gm. on the side with the narrow crush and 3·28 gm. on the side with the extensive crush. Some differences in the thresholds occur, for the coil distance above the crushes was 92 cm. on the side with the single narrow crush and 56 cm. on the side with the extensive crush. These data suggest that the reason for the differences may be found in an insufficient number of the nerve fibres re-connected with appropriate pathways on the side with the extensive crush. There is, however, a clear indication, even from these few experiments, that the final level of recovery reached after these long crushes is better than that obtained after a suture, for in the former the longitudinal pathways in the nerve are preserved at least to a considerable extent.

Recovery after a second interruption.—In a series of animals the process of recovery has been followed after the nerve has been twice interrupted. In each

rabbit the peroneal nerve has been crushed or cut and sutured on one side near its entry into the muscles. In the animals in which the nerve had been crushed another operation was performed either before (8 and 16 days after the first operation) or after motor recovery (42 days after the first operation). In the animals in which a suture had been performed the second operation was undertaken after motor recovery (61 days after the first operation). The second operation has consisted in all cases in crushing the peroneal nerve on both sides at the same level above the first interruption (about 30 to 40 mm. from the M. peroneus longus). The distances have been controlled with care by measurements made at necropsy. The results show that the onset of recovery has been quicker on the side with the second lesion (see Table I) when the first interruption has been a crush of the nerve. Little difference, however, has been found when the interval between the two operations has been only 8 days. On the other hand a constant difference has been found if the interval between the operations has been 16 or 42 days. On the side with two interruptions the degree of recovery has followed the normal sequence, the only difference being that a normal degree of recovery has been achieved at a later time corresponding to the later onset of recovery. But in two animals in which the second operation has been performed 42 days after the first interruption the degree of spreading became less in, one animal as far as degree 1, about a month after full recovery. No explanation for this strange phenomenon is available.

TABLE I.—TIMES IN DAYS OF RECOVERY AFTER SECOND INTERRUPTION OF THE PERONEAL NERVE

Animal	Kind of first operation	Recovery after first operation	Interval between first and second operation	Motor recovery on	
				Twice operated side	Control side
714	Crush	—	8	24	25
715	Crush	—	8	25	25
578	Crush	—	16	31	34
687	Crush	—	16	27	32
709	Crush	—	16	32	34
579	Crush	24	42	25	28
674	Crush	23	42	30	32
668	Crush	24	42	26	29
584	Suture	50	61	40	35
706	Suture	34	61	40	35
707	Suture	39	61	35	31

In the 3 animals in which the nerve has been cut and sutured at the first operation, recovery of motor function has been delayed after the second interruption. The degree of spreading has been similar to that usually seen after sutures, namely, degrees 2 and 3. However, as in the animals with late second interruption, there has been a regression in the degree of spreading. Originally it was thought that the difference in the degree of muscle atrophy due to the first denervation would retard the time of onset of functional recovery. That there is such a difference is seen on comparing the weights of the muscles of the two sides. But the greater atrophy does not, apparently, alter the earlier onset of recovery in the animals with the second reinnervation. From these results it is clear that it is easier for motor fibres to bring about a re-establishment of function after a second interruption, if both interruptions are made by crushing. It seems probable that this is due to the fact that after a second interruption more motor fibres arrive at the end organ. After an interruption of a nerve branching of fibres occurs (Watrous (1940), Howe, Tower and Duel (1937)), and more fibres are found in the peripheral stump than in the central stump in the early stages. Presumably after a second interruption these extra fibres degenerate again and there is further multiplication of Schwann cells. As there is an excess of Schwann bands in the peripheral trunk and in the muscle itself the new fibres have a greater chance of finding suitable pathways. At a given time more fibres may thereby arrive at the end organ permitting the earlier initiation of recovery of motor function after the second interruption. The correctness of this explanation is shown by the fact that, when the second interruption after the first crush is performed after an interval of 8 days only, i.e. at a time when few fibres have yet entered the peripheral stump, no clear difference is to be observed in the time of recovery.

Recovery and interruption of blood supply.— In 3 animals the nerve has been crushed high up in the thigh on both sides and on one side the popliteal artery and vein ligatured and cut. Time of onset of recovery has been recorded after 43, 42, and 40 days on the side without ligature and after 45, 42, and 43 days on the side with the ligatured vessels. There has been no marked difference in the spreading index at the time of necropsy, i.e. 3 months after the operation; but in the first week after reappearance of function slight differences could be observed. At necropsy differences in the weight of the muscles have been found, the weight of the M. extensor digitorum being 1·60, 2·50, and 1·78 gm. on the side without ligature of the vessels and 1·22, 2·02, and 1·57 gm. on the side with ligature. Thus the ligature of the popliteal vessels does not seem to have a significant effect on the time and quality of motor recovery although the effect of the ligature is indicated by a greater muscle atrophy. It appears that devascularization of the muscle by ligature of these vessels is incomplete, and that other vessels are sufficient to prevent serious damage to the muscles.

Recovery after cross unions.—In a number of experiments the central stump of the tibial nerve has been sutured to the peripheral stump of the peroneal nerve. Recovery of spreading has been seen in all cases in which the animals have been observed for a sufficiently long time. The time of onset of recovery has been approximately the same

as after primary suture of the peroneal nerve. The variations are smaller than in ordinary sutures. This may be due to the fact that the sutures in cross unions are easy to perform as a long stretch of nerve is available and retraction can be avoided. But the degree of recovery is very poor indeed and spreading can usually be demonstrated only when the animal is held upside down, and then with some difficulty. The degree of spreading has never exceeded degree 2 and in many cases spreading of the 4th toe alone has been observed. In no case has dorsiflexion of the foot been seen with any certainty. This is the more interesting as in all cases stimulation of the tibial nerve produced dorsiflexion. Absence of suitable central connections must therefore be the explanation of the absence of this movement as a reflex function. In other experiments the central stump of the peroneal nerve has been sutured to the peripheral stump of the tibial nerve. No recovery of spreading of the 1st toe has been observed after this procedure, though stimulation of the peroneal nerve has shown clear contraction of the muscles innervated by the tibial nerve.

There is little doubt that some recovery of function follows the crossing of mixed nerves (Rawa (1885), Howell and Huber (1892), Kennedy (1913), Osborne and Kilvington (1911)). Much more controversial is the question of whether normal co-ordinated movements of hetero-innervated structures takes place following cross unions. Earlier authors (Kennedy (1913), Osborne and Kilvington (1911)) have claimed that readjustment may take place, but their views have been strongly criticized by Cunningham (1898) and Sperry (1941)). Watrous and Olmsted (1941), however, have shown that some such readjustment does indeed take place, although it is by no means complete. The experiments described here do not in themselves prove that after cross unions of nerves a central readjustment takes place, since the tibial nerve carries fibres to the M. abductor hallucis which contracts during the spreading reflex of the normal animals, and these fibres, innervating the M. peronei II, III, and IV, would thus be available to produce reflex spreading of the toes following tibial-peroneal cross unions. On the other hand, the absence of any reflexly elicited dorsiflexion of the foot suggests that little readjustment is possible.

Recovery after delayed suture.—The question if and to what degree the time and extent of motor recovery is influenced by a delay in suturing is of great clinical importance. Experimentally the problem is difficult to approach, since, in order to maintain the denervation, a long stretch of nerve must be resected and this fact makes a later suture of the two stumps under standard conditions impossible. In the experiments to be described an attempt has been made to approach the problem by use of cross unions.

At a first operation the peroneal nerve has been cut and resected over a long stretch to make reunion impossible. Even this procedure has not proved satisfactory; in one case it was found at a further operation that union had taken place. Therefore in later experiments the central stump has been injected with 20 per cent. formalin to prevent any reunion. After varying intervals of time (1, 2, 4, 6, and 8 months) the tibial nerve has been cut and its stump sutured with plasma to the peripheral stump of the peroneal nerve. At the same time a primary suture of the tibial nerve into the peroneal nerve has been performed on the opposite and control side. This method of bridging a gap has the advantage that a suture may be performed under ideal conditions since a long stretch of nerve is available and retraction can be avoided. But the quality of recovery is poor, for the degree of spreading obtained even on the control side (see above) is only 1 or 2. Nevertheless this technique provides a method for studying effects of delay in suturing. A necropsy has been performed in every case 3 months after the second operation, at times varying from 9 to 35 days after recovery.

The results of the experiments are given in Table II, together with the times of onset of recovery in two further control cross unions. These experiments show that there is no considerable difference in the time of onset of recovery of motor function after denervation up to 6 months. However, in every case the recovery has been a little later on the twice-operated side, the average time of recovery being 56 days on the control, and 65 days on the twice-operated sides. In the animal with the longest time of denervation (8 months) the difference is more considerable than in the others (1 month). The data suggest that onset of motor recovery begins to be seriously postponed after a period of 6 months. In all cases the side with the primary suture has shown a higher degree of spreading, a difference increasing with the longer time of denervation. As expected, there have been clear differences in the trophic state of the end organs, as indicated

TABLE II.—RECOVERY AFTER CROSS UNIONS OF TIBIAL INTO PERONEAL NERVE, MADE AFTER THE PERONEAL NERVE HAS BEEN ALLOWED TO DEGENERATE FOR VARYING PERIODS. THE LAST TWO COLUMNS INDICATE THE THRESHOLDS TO FARADIC STIMULATION OF THE NERVE ABOVE THE JUNCTION

Animal	Months before secondary suture	Onset of recovery in days		Weights of M. tibial. ant. (gm.)		Thresholds coil distance (cm.)	
		Twice operated side	Control side	Twice operated side	Control side	Twice operated side	Control side
642	1	57	55	1·65	1·75	—	—
650	2	74	56	0·79	1·42	42	48
680	4	60	58	1·22	1·74	58	59
595	6	60	53	0·81	1·08	54	62
597	6	55	50	0·84	1·40	38	66
581	8	81	50	0·97	1·42	39	66
606	—	—	66	—	—	—	—
587	—	—	65	—	—	—	—

by the weights of the muscles and state of the skin. The thresholds of the nerve have been examined above and below the suture at the time of necropsy, and have been found to be higher on the twice-operated side. However, the differences are considerable only after long periods of degeneration. The fact that the threshold above the junction is higher after secondary suture presumably indicates that fewer fibres have reached the muscle. This, agreeing with the smaller degree of function which returned, indicates one of the possible disadvantages of delay in suturing peripheral nerves (Young, 1942).

Effect of infection on recovery of function.—No special experiments have been undertaken to study the effect of infection on the process of recovery, but some observations on animals accidentally infected allow some conclusions. The infections, found in these rabbits, have been abscesses produced by *Staphylococcus aureus*, and either confined to stitches or going deeper between fascia and muscle. Other cases have shown superficial suppuration of the skin. Abscesses confined to stitches or superficial suppuration of the skin, as observed in 10 animals, had no significant effect on the time or quality of recovery. However, in a case in which there was a large abscess compressing and partly infiltrating one peroneal nerve following interruption by crushing of the nerve on both sides no recovery of motor function was observed on the infected side, whereas on the other uncomplicated side recovery of spreading was recorded after 58 days. This is a later time of recovery than has been observed in any other case with a lesion at this level (distance from point of lesion to M. peroneus longus 78 mm.). Therefore the abscess compressing and infiltrating the one nerve has not only prevented recovery on the infected side but has also delayed the process of recovery on the opposite and uncomplicated side. On the other hand, in another animal in which the peroneal nerve had been crushed on both sides at the same level, a severe lymphangitis developed on the left side, with a bulbous œdema of the skin of the leg and a hydrocele. The animal recovered from this infection. In spite of these conditions recovery of spreading was observed after 38 days on the infected and after 40 days on the uncomplicated side. This is a rather quick recovery on the infected side, and as sensory recovery was also quicker on the side with the previous infection the latter has certainly not delayed the onset of recovery.

Effect of age on recovery.—Gutmann *et al.* (1942) have shown that the rate of advance of functionally completed motor fibres in animals about one month old is markedly higher than in adults, being 5 mm./day after crushing the peroneal nerve, giving a mean latent period of 10·2 days. Results of 5 further experiments in animals of this age can now be added. The peroneal nerve was crushed at different levels and recovery of spreading recorded after 10, 12, 17, 18, 19, 19, 20, 20, and 21 days, the corresponding distances to the M. peroneus longus being 5, 4, 40, 34, 44, 34, 30, 38, and 31 mm. No exact measurement of the distance is possible in such young and quickly growing animals. Usually the distance has been measured at necropsy at time of recovery, but in a few cases the necropsy was performed several weeks after recovery and then the mean value between the measurement at operation and that at necropsy was taken. Comparing these data with recoveries in adult animals in which the lesion has been made at a corresponding level the clear difference in the speed of recovery may readily be seen.

In a series of young animals the onset of recovery of indirect excitability has been tested. After crushing the peroneal nerve in the middle of the thigh, return of excitability has been found after 13 days. Moreover, the thresholds in the peripheral stump have become lower at a much earlier time than in adult animals. Observations on the quality of recovery indicate that the spreading index degree 4 is achieved at a quicker time than in adult animals, normal spreading being observed about 5 days after first reappearing.

In contrast to this speedy recovery in young animals recovery in old animals has been found to be especially slow. The youngest animal of a series of large animals in which the peroneal nerve was crushed high up in the thigh actually showed an especially quick recovery. Old animals in the series with crush lesions of the peroneal nerve all showed a relatively late recovery. It is more difficult to show the effect of age on recovery in the series where the peroneal nerve has been cut and sutured as this process introduces such great variations. The oldest animal in the series showed macroscopically a good suture. No recovery occurred even after 71 days, therefore a biopsy was performed, but stimulation of the nerve produced contraction of all muscles. Recovery was then recorded 79 days after the operation. The recovery was very late on both sides.

Discussion

Recovery of a muscle is a very complex and prolonged process. It sets in with the reinnervation of the muscle by the first regenerating fibres. This stage is of course a necessary preliminary to recovery, but must not be identified with the recovery of the muscle as a functioning entity. It seems necessary to state this since estimates of the rate of growth of nerve fibres have often been deduced from data on recovery of function. Thus data obtained by Vanlair (1894) from recovery of function have been freely interpreted as estimates of the rate of growth of nerve fibres. But as has been demonstrated elsewhere (Gutmann *et al.*, 1942), the return of function does not provide a test for the estimation of the rate of advance of the regenerating axon tips.

The fact that a muscle is reinnervated before functional recovery appears is demonstrable not only by histological methods, but also by trophic

changes in the muscle. Thus the increase of circumference and the decrease of the thresholds of the muscle to direct stimulation appear before functional recovery. At this stage the muscle does not yet respond to stimulation of the nerve. The gradual increase in the "tone" of the paralysed muscles before any signs of voluntary contraction appear has been clinically observed (Stookey (1922), Tinel (1917)). This observation and others led Hunt (1918) to postulate two sets of motor fibres such as Head, Rivers and Sherren had done for sensory fibres. These two sets of fibres, belonging to the "neo and paleokinetic motor systems," were considered to regenerate at different rates. But the difference in time between arrival of fibres in the end organ and functional recovery suggests that a process of functional completion (Gutmann *et al.*, 1942) must ensue before the regenerated fibres are able to conduct impulses in such a way that contraction of the mass of muscle fibres, visible as a movement, is possible. This process is a very complex one and includes maturation and increase in number of nerve fibres in the end organ, and possibly also central adjustments. A certain number of sufficiently mature fibres must be present before function returns. Apparently the first regenerating axons are able to produce certain trophic changes, but they are either not sufficient in number, have not yet formed proper connections, or they are not yet in a sufficiently mature state to allow return of function.

At a further stage of functional completion the muscle becomes excitable to electrical stimulation of the nerve. Holobut and Jalowy (1936) found return of excitability through the nerve after cutting the sciatic nerve in rats about 28 days after the operation. Howell and Huber (1892), after cutting and suturing the ulnar nerve in dogs, gave the time as 21 days. It is difficult to compare these data with those of the present series as no measurements of the distances from the lesion are given. Onset of indirect excitability will of course vary according to the level of the lesion, and with the method of interruption of the nerve.

Onset of indirect excitability does not imply recovery of function. A further stage of functional completion is necessary before this appears. Thus in cases of unaided union return of excitability is more often observed than actual functional recovery (Gutmann and Sanders (1942)). Excitability of the nerve through the skin appears in these experiments about 1 week after the beginning of recovery, indicating a further stage in the maturation of the nerve. In human cases faradic excitability of the nerve through the skin generally appears a considerable time after the return of voluntary contraction, the longer delay being presumably explained by the greater thickness of the skin.

The process of recovery is not finished with the first return of a movement. The degree of movement, indicated by the spreading index in these experiments described in the preceding pages, increases for some time. Even after the full extent of movement has returned the regeneration is still incomplete, for the muscle continues for some weeks to increase in weight (Fig. 6), the rate of this increase presumably depending on the amount of use of the limb. Moreover, the nerve fibres themselves continue to increase in diameter for many months after functional recovery is apparently complete (Sanders and Gutmann, 1943). The question, therefore, arises—is complete functional recovery in the sense of establishing the same conditions as before the operation ever achieved? After suture the physiological test itself shows that recovery is never complete. Further, Sanders and Gutmann (1943) have shown that even 1 year after suture differences in diameter and number of fibres between central and peripheral stump are still great.

Delay in recovery when a long interval is left between injury and operation has been observed by many authors (Stookey (1922), Spielmeyer (1915), Lewis (1920)). On the other hand, Katzenstein (1913) reported successful recovery after 14 years, and Stopford (1920) stated that if sepsis can be excluded a delay of 12 to 18 months has no effect on the time of onset and on degree of recovery. The question of nervous regeneration after delayed sutures has been studied by Holmes and Young (1942), who have shown that it is not the power of outgrowth which declines after a delay but that changes in the peripheral stump occur which definitely prejudice the maturation of the regenerating nerve fibres. The experiments here described indicate that the degree of recovery is worse after a delay before suturing and that differences in onset of recovery begin to be especially apparent after a delay of 6 months. The reasons are not only the changes in the peripheral stump but also in the end organ. These changes in the muscle are partly irreversible and will by themselves lead to a bad functional result.

Some discussion is necessary of the speed of regeneration and the factors influencing it. The constancy of the time at which recovery has appeared after lesions close to the muscle enables one to estimate that in adult mammals it is not likely that any recovery by outgrowth of new fibres occurs in less than about 15 days, however close the lesion is to the muscle. Recoveries in shorter times than this must be a result of incomplete interruption of the nerve or of trick movements.

The question whether recovery proceeds relatively more slowly with greater distance between lesion and end organ has been much discussed, but very few critical data are available. Stopfordl (1920) concluded that recovery proceeds relatively more slowly in distant lesions. This would of course be expected since latent periods at the suture line and in the muscle occupy a relatively greater time than in the closer lesions. Foerster (1929), however, held that the longer fibres were more vulnerable, being readily damaged in dissociated lesions, and that the same principle applied during recovery. Both of these facts would be explained if a relatively

greater degree of maturation was necessary to reach functional completion after the more distant lesions. However, extensive investigation of times of recovery after lesions at different distances from the muscles have failed to show any relatively greater delay following more distant lesions (see Fig. 8). But it is possible that some effect of the level of the lesion would become apparent when longer distances are considered. In fact, when considering data from recovery of sensation on the foot of the rabbit after crushing the peroneal nerve, the plotting of time of final recovery against the distance of the lesion seems to indicate some relatively greater delay after the more distant lesions (Gutmann and Guttmann, 1943). Longer distances of the nerve have to be reinnervated during recovery of the skin, and therefore there is greater opportunity for the effect of distance on regeneration to be shown.

Some authors (Howell and Huber, 1892, Stookey, 1922) have discussed differences in the speed of recovery of sensory and motor function. Decision on such questions is only possible if the distances from the lesion to the end organs are measured. After interruption of the peroneal nerve in rabbits motor recovery always sets in before sensory recovery, but this is to be expected, since the distance to the skin is longer than to the muscles. But the distance is not the only factor which has to be kept in mind. Although we may consider that the rate of growth of the tips of sensory fibres is the same as that of the motor fibres, this does not imply that the rate of functional completion is the same in both cases. One might expect that functional completion would be achieved more quickly in pain fibres, as these have a smaller diameter. Indeed, after crushing the peroneal nerve the apparent rate of advance of functional completion of motor fibres is 2·77 mm./day, that of pain fibres 3·35 mm./day (Gutmann and Guttmann, 1943).

Differences in speed of recovery after crushing and after suturing might be best explained by the differences in the scar, the result being that less fibres and presumably less matured fibres arrive at the end organ at a certain time. In this connection the fact that a longer time elapses between arrival of fibres and onset of excitability after suturing than after crushing is of interest.

That the rate of functional completion of the nerve is not fixed is shown by the surprising fact that recovery occurs quicker after a second interruption of a nerve. The possible explanation of this is the advantage given by the surplus of Schwann cells produced by the second interruption.

These data all show that other factors besides the rate of growth of the tips of nerve fibres must be considered if estimates of speed of recovery of function and factors influencing it are to be discussed. They indicate again that recovery of motor function is a complex and prolonged process and cannot be adequately discussed in terms of a narrow concept of the process of regeneration merely as an outgrowth of axons.

Summary

1. A good test of the time and degree of functional regeneration of nerve is provided by a study of the recovery of the function of spreading of the toes of the rabbit, following lesions of the peroneal nerve.

2. After crushing the peroneal nerve at the knee fibres return to the muscle after about 10 days, contraction on stimulation of the nerve after about 18 to 20 days, first reflex function after about 25 days. Full reflex function is achieved 8 days later.

3. For a time after recovery from crushing the nerve spreading of the toes may be greater than normal.

4. The circumference of the denervated muscle begins to increase, and its threshold to direct stimulation to decrease, before reflex function, and sometimes before even indirect excitability return.

5. Fibrillations continue in the muscles for about 2 weeks after reappearance of reflex function.

6. The normal weight of the muscles is nearly regained 12 weeks after reappearance of reflex function following crushing of the peroneal nerve.

7. Study of recovery after crushing the peroneal nerve showed that when the lesion is more distant there is a longer delay between arrival of fibres at the muscle and the appearance of excitability through the nerve. The time between the beginning of recovery and its completion is greater after more distant than after near lesions.

8. From a study of recoveries in 69 cases where the nerve was crushed at different levels the rate of advance of regeneration down the nerve is given as $2{\cdot}77 \pm 0{\cdot}09$ mm./day after a latent period of 18·2 days. The rate is not slower with more distant lesions.

9. After severance and suture all the processes of recovery are slower than after crushing the nerve. The rate of advance of regeneration is $1{\cdot}69 \pm 0{\cdot}34$ mm./day after a latent period of 27·7 days. The delay between arrival of fibres at the muscle and return of reflex function is greater than after crushing. After the first appearance of reflex function it increases only gradually in amount and never returns to normal.

10. Recovery after crushing the nerve over a length of 4 cm. is later and less complete than after a local crush, but is more satisfactory than after severance and suture.

11. When the nerve is crushed a second time 16 or 42 days after an initial crush near the muscle the recovery occurs slightly earlier than after a single crush. This difference is not seen when the interval between the crushes is 8 days.

12. Ligature of the popliteal vein and artery does not delay recovery of the muscles following interruption of the peroneal nerve.

13. After union of the central stump of the tibial nerve with the peripheral stump of the peroneal nerve some spreading of the toes returns. This

does not imply central relearning since the tibial nerve contains some fibres which innervate muscles normally producing spreading.

14. Tibial-peroneal cross unions have been used to test the effect on recovery after a delay between injury and suture. In all cases such a delay has been found to retard recovery, but the effect has only been marked when the delay has exceeded 6 months. The degree of recovery has been reduced by delay in suture.

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CEREBELLAR EXTRADURAL HÆMATOMA *

BY

F. K. KESSEL

THE clinical features of an extradural hæmatoma due to rupture of the middle meningeal artery are well known; the " classical " picture may, however, be frequently absent or overshadowed by the signs produced by single or multiple cerebral lesions by a second extradural or a subdural hæmatoma. Besides the meningeal arteries the great venous sinuses can produce intracranial hæmorrhages. If a tear involves such a sinus and gives rise to an extradural hæmatoma overlying one of the more or less " silent " cortical areas, early diagnosis may be very difficult. To this latter group belongs the extradural hæmatoma of the posterior fossa; probably the rarest form of traumatic intracranial bleeding. The present paper contains a description of such a case, which was under the writer's care in spring, 1938.

A girl, aged 24, was thrown off her bicycle by a blow from an opening door of a stationary car, which she was about to pass. She struck the back of her head heavily, fell, and lost consciousness for a few minutes. Later she vomited, but on admission to hospital shortly after the accident she only complained of severe headache. There were no external injuries and no neurological abnormality was detected. X-ray pictures showed a slight separation of the left half of the lambdoid suture. About 30 hours later an experienced ward-sister observed the patient in a series of typical " cerebellar fits." In these her head was well retracted and her extremities rigidly extended; she was cyanosed, her breathing was irregular and she rapidly became unconscious. The first attack lasted about 2 minutes, a second one occurring a few hours later, and a third prolonged and severe attack was observed on the morning of the third day. After the first attack the patient's condition, which had been satisfactory until then, changed for the worse. She became increasingly restless and finally comatose. A lumbar puncture was performed, but only a few drops of clear cerebro-spinal fluid were obtained, the flow then ceased abruptly. A second puncture, performed 2 hours later, yielded the same result. There was no nystagmus and the tendon reflexes were equal on both sides.

The history of trauma, the separation of the left half of the lambdoid suture, the cerebellar fits, the cerebro-spinal fluid block, and the increasing coma all pointed to a hæmorrhage in the posterior fossa, probably extradural. Owing to the patient's deterioration operation could no longer be delayed.

Operation.—The usual skin-muscle flap for cerebellar exposures was employed and a burr-hole made over each cerebellar hemisphere. On the left side an extradural hæmatoma was found, and in order to evacuate it, the greater part of the bone on this side had to be nibbled away. A hole was then discovered in the left transverse sinus, situated at about the middle of its lower border—undoubtedly the source of the bleeding. The tear had already been closed by clot, and no further bleeding occurred. The hæmatoma had covered the greater part of the dura over the left cerebellar hemisphere, which was flattened and shifted to the right, thus blocking the cisterna magna. In order to relieve the increased intracranial tension, the cisterna was opened wide and fluid escaped under considerable pressure. Future events were to cause anxiety as regards this opening. The patient's general condition rapidly improved towards the end of the operation.

The healing of the wound was troublesome. Two days after the operation necrosis of the superficial layers of the scalp at the back of the head began and soon a great portion of the incision was involved in this process. A persistent leakage of cerebro-spinal fluid ensued, and apart from frequent dressing of the wound little could be done to check the flow of fluid. Fortunately the fistula closed spontaneously, and within a few weeks the patient left the hospital in good condition.

Comment

When first confronted with this case we had, like McKenzie (1938) under similar circumstances, been unaware of the occurrence of extradural hæmatomata in the posterior fossa, but our doubts regarding the diagnosis were dispelled by the striking signs presented by the patient.*

The most outstanding clinical feature was, of course, the patient's fits, which, like the occurrence of extradural cerebellar hæmatomata and the prognosis of a rupture of a transverse sinus, need some further comment.

Rigid Fits

The patient's fits were similar to those observed in cases of cerebellar tumours, described for the first time by H. Jackson (1906) and commonly called " cerebellar fits "; they are mostly considered as a special form of decerebrate rigidity caused by a

* Read at the 28th meeting of the Society of British Neurological Surgeons (20th July, 1941, Oxford).

* In the discussion following the reading of this paper Prof. Cairns mentioned a case of his own in which the clinical picture suggested cerebellar bleeding; the condition, however, resolved spontaneously. He went on to suggest that the Queckenstedt test might yield useful information in cases of this type, particularly when the lateral sinus has been ruptured. In the present case this test could not have been carried out owing to the almost complete block which existed.

functional decerebration at a level near the junction of pons and medulla. In Sherrington's (1897, 1898) opinion fits of this kind produced in animals are release phenomena arising from the interruption of cerebellar efferent impulses from the anterior lobe and its nuclei. Why these attacks are paroxysmal is not known. Webster and Weinberger hold the opinion that "cerebellar fits" are an extreme form of physiological decortication due to a temporary cortical ischemia. Penfield and Erickson (1941) state that "cerebellar" fits have nothing to do with the cerebellum itself and result from activity within the brainstem, namely a sudden neuronal discharge within the upper pons or lower mid-brain.

Besides this type of decerebrate rigidity two other forms can be distinguished in man and higher animals, namely, a "high" and a "low" decerebration; their characteristics and origin have been thoroughly discussed by Fulton (1938). Their essential symptomatic difference lies in the attitude of the upper extremities, which in a "high" decerebration are semiflexed and which show the tonic neck and labyrinthine reflexes of Magnus and de Kleijn, whereas in a "low" decerebration the upper extremities are in a rigid extension with pronation, and the rigidity may be so intense that the above-mentioned reflexes are difficult to elicit. Moreover, Bailey, Buchanan, and Bucy (1939) have recently stressed the important fact that an intercollicular ("low") decerebration results in relatively the same picture in all mammals—i.e. a generalized and severe extensor rigidity and an absence of the righting reflexes—but that the production of a high decerebrate syndrome demands a quite different level of section in the carnivora and the primates. In primates the high decerebration is essentially produced by decortication restricted to the areas 4 and 6, and the picture thus produced is, therefore, identical with a complete bilateral hemiplegia.

After Sherrington's description of decerebrate rigidity in 1897 and 1898 more than two decades passed before these results of experimental research were correlated with, and applied to, clinical observations. Apart from a few scattered reports, Wilson (1920) was the first to analyse certain postures in terms of decerebrate rigidity. Since then a number of cases of brain tumour showing decerebrate (or decorticate) syndromes have been reported (e.g. Walshe (1923), Davis (1925), Bailey (1933), Bailey, Buchanan, and Bucy (1939), and others), the tumour being mostly situated in the diencephalon or the hypothalamus. Certainly more cases of this kind have been observed than have been published; thus the present writer has seen the phenomenon under discussion in two cases of pineal tumour.

In cases of head injuries, also, states of muscular rigidity can be observed. It is perhaps worth mentioning that Jacobson's (1885) classical paper on middle meningeal hæmorrhage contains two cases with general muscular rigidity. Jefferson in 1921 described two cases with anteriorly placed clots derived from the middle meningeal arteries. The patients exhibited bilateral limb rigidities. Jefferson was apparently the first to describe this condition as a definite entity after head injury, and regarded it as the nearest approach to true Sherringtonian decerebration possible in man. Since then further observations of this kind have been made (Babcock (1928), Woodhall and co-workers (1941), Penfield and Erickson (1941)), and a careful study of the extensive literature on head injuries would probably bring to light many more.

As to the cause of decerebrate rigidity in cases of intracranial hæmorrhage different explanations have been given: anoxæmia or change in intracranial circulation produced by the injury (Jefferson 1921, Babcock (1928), Penfield); or a temporal pressure cone (Jefferson, 1938); or compression of the mesencephalon (Reid and Cone, 1939). In my case, the space-occupying hæmatoma in the posterior fossa and the at least partial obstruction of one lateral sinus must have disturbed the intracranial circulation to a considerable extent, and this could, therefore, very well explain the whole phenomenon if one is not inclined to believe that the indirect pressure of the hæmatoma upon the anterior lobe of the vermis had a release effect in Sherrington's sense.

It is, however, important to realize that other patterns of fits may be caused by a lesion in the posterior fossa. Jackson (1906) quoted reports of clonic convulsive movements in patients with cerebellar tumours and other cases have been described since. Lately Webster and Weinberger have shown that in cases of cerebellar tumour practically all the kinds of fits usually observed in supratentorial lesions may occur.

The occurrence of rigid fits in head injuries emphasizes the seriousness of the prognosis (Babcock (1928), Woodhall (1941)) and indicates the urgent need for surgical intervention.

Extradural Venous Hæmorrhages

There are three possible sources of extradural hæmorrhages, namely, the meningeal arteries, the diploic veins, and the venous sinuses. Extradural hæmatomata of venous origin are by no means rare. Wood-Jones (1912) went so far as to say that from the published accounts of operations undertaken for middle meningeal hæmorrhage and from his own investigations it would seem that in the majority of such cases the blood was issuing from a ruptured venous sinus rather than from an artery. Surgical experience since then has not confirmed this view. Nevertheless, not a few cases have been reported illustrating the occurrence of venous extra-dural hæmorrhage (Erichson (1878), Jacobson (1885), Verbruggen (1937), McKenzie (1938), Reichert and Morrissey (1941), Munro and Maltby (1941), and others).

Only very few cases of extradural cerebellar hæmatoma have been made known; none of them had been successfully operated upon, at the time I encountered my case. Since then, Coleman and Thomson (1941) have reported a further case.*

* As these authors state they have not found a case in the literature that recovered, reference should be made of a previous communication (Jaeger and Kessel, 1938), in which the present case was mentioned (p. 140).

The following cases of extradural hæmatoma in the posterior fossa have been found in the literature: Lecount and Apfelbach, Naz and Jaboulay, Vance, McKenzie, Coleman and Thomson. It will be seen that not all of these cases can be considered as true " extradural cerebellar hæmatomata." A few other cases of hæmorrhage in the posterior fossa, complicated by other lesions, will be mentioned later.

Lecount and Apfelbach (1920) reported on 504 autopsied cases of injuries of the brain and the cranial bones. One hundred and ninety-nine cases showed extradural hæmatomata, 104 of them, weighing 20 to 246 g., had been large enough to produce an appreciable compression of the brain. There were no less than 8 cases with fractures of the posterior fossa with hæmorrhages from one of the transverse sinuses, the blood clot in none of these cases weighing more than 50 g. Unfortunately no further details about these 8 cases can be found in this very valuable paper. I very much doubt that all of them could be correctly designated as " extra-cerebellar hæmatomata," if this term means a hæmorrhage for the most part or wholly restricted to the cerebellar fossa proper. If out of 104 major extradural hæmatomata 8 were situated over the cerebellum, a ratio of 12 supratentorial hæmorrhages to 1 infratentorial would exist in the authors' collection. This is in striking contrast to all clinical experiences and to all other reports concerning extradural bleeding. I assume, therefore, that at least some, perhaps the majority, if not all, of these 8 cases of Lecount and Apfelbach were actually cerebellar-occipital hæmatomata. But it is noteworthy that all these 8 hæmorrhages were due to rupture of one of the transverse sinuses and that all of them were accompanied by fractures of the skull.

In his monograph Duret (1922) mentions 2 cases of " hématomes extra-dure-mèriens des fosses cérébelleuses," one observed by Bousquet (1901) and another by Naz and Jaboulay (1910). In all probability, however, these hæmorrhages were not in the cerebellar fossa proper but over the occipital lobes.

Vance (1927) reported on 512 autopsies of skull fractures, 106 of them with extradural hæmorrhages; 4 of the hæmatomata were caused by a ruptured transverse sinus and had " pressed on the cerebellum and occipital lobes." This description seems to show rather clearly that these cases were not pure " extra-cerebellar hæmatomata." But it is again remarkable that all these cases had fractures of the posterior fossa and ruptures of the transverse sinuses.

The first certain extradural cerebellar hæmatoma was described by McKenzie (1938). McKenzie's collection of 20 cases of extradural hæmorrhage contained an account of one case of extradural hæmorrhage over the right cerebellar hemisphere. This patient, a child, sustained a slight head injury. There was a lucid interval of 30 hours, and marked flaccidity of all limbs was the only abnormal neurological feature. The cerebrospinal fluid was clear. Forty-four hours after the injury and 14 hours after the onset of stupor the patient died from respiratory failure during an epileptic seizure beginning on the right side of the body and followed by opisthotonus. Necropsy disclosed a fracture of the occipital bone one inch long, which had not been seen on the X-ray films, and a clot compressing the right cerebellar lobe. Commenting on this case, McKenzie remarked that an operation might have saved the patient's life. He does not discuss the source of the bleeding, but clearly it could not have come from the middle meningeal artery, and may have been venous.

The case described by Coleman and Thomson (1941) is of great interest. The patient, a negro child, aged 9, had fallen from a moving truck, striking the back of his head, without becoming unconscious. He was brought to the hospital, but discharged, as there were no other signs present but a small hæmatoma in the left occipital region. The boy was returned to hospital 24 hours later because of headache and some drowsiness; he had vomited once or twice. The examination was again negative and the child was again discharged. The following night he was brought the third time to the hospital; he was moderately drowsy, occasionally very restless, complained of headache, and had vomited several times. The patient was then admitted to the hospital for further observation.

Fifteen hours later (on the morning of the third day following the accident) the boy was very drowsy, his neck was stiff and all limbs showed definite hypotonia. The biceps, triceps, knee and ankle jerks were absent. X-ray examination of the skull showed a long linear fracture in the mid-line, extending from the lambdoid suture downward into the foramen magnum.

Operative intervention revealed the presence of some old blood and of an early organized extradural hæmatoma over both cerebellar hemispheres, apparently due to a laceration of the torcular Herophili. The hæmatoma was removed and the patient recovered completely.

In this remarkable case more than 60 hours passed before the first symptom—drowsiness—appeared. Coleman and Thomson explain this long interval by the fact that the pressure within the sinus is only 4 to 6 mm. Hg., and that therefore a hæmatoma from a torn sinus develops slowly. A rather long latent period may therefore intervene between the time of injury and the onset of symptoms—an important point in view of the diagnosis.

Coleman and Thomson quote in their communication an unpublished case observed by Mayfield; the patient was suspected to have a cerebellar clot, but died before the posterior fossa could be explored. The post-mortem examination revealed an extradural cerebellar hæmatoma.

This short review of the literature shows that uncomplicated extradural cerebellar hæmatomata are extremely rare. The cases of McKenzie, Coleman and Thomson, Mayfield, and my own case, belong certainly to this group, but the cases quoted

by Duret are most probably not cerebellar hæmatomata, and it seems to be very unlikely that all 8 cases mentioned by Lecount and Apfelbach were pure posterior fossa hæmorrhages. None of Vance's cases apparently belongs to the group under discussion.

No other cases of uncomplicated extradural cerebellar hæmatoma could be found in the literature, but cases have been reported in which the extradural hæmatoma in the posterior fossa constituted only part of the pathological findings. Duret quotes a few cases of this kind. Two further cases of special interest as to the source of the bleeding may shortly be mentioned. Munro and Maltby (1941) in their series of 44 cases of extradural hæmorrhage reported one cerebellar hæmatoma found at post-mortem examination. Reporting this case in an earlier publication Munro (1938) stated that the hæmorrhage was caused by rupture of tributary veins to the left transverse sinus. Complicating this condition were: a right supratentorial subdural hæmatoma, contusion and laceration of the brain, fracture of the left occipital bone and medullary œdema. The clinical signs were naturally manifold and led to an operation on the subdural hæmatoma, while the bleeding in the posterior fossa remained unsuspected. The patient died 39 hours after the injury.

Pringle (1938) reported 71 cases of intracranial hæmorrhage. One of these (No. 267) was unconscious when admitted to hospital. A hæmatoma was suspected, but not found at operation. Autopsy disclosed two separate clots, one over the left occipital lobe and another over the left cerebellar hemisphere. Several fractures of the skull, cerebral contusion, an intracerebral and a subdural hæmorrhage were also present. Obviously no exact clinical diagnosis could have been arrived at in so complicated a case.

In another quite different type of case, hæmorrhage from the middle meningeal artery may extend backwards over the cerebellum. Kroenlein (1895), McKenzie (1938), and other authors have described such cases. Most of these patients died.

Munro (1938), Ricard (1929), and Voris (1940) have each observe and successfully operated upon a case of extradural hæmatoma originating from a tear in the upper edge of the transverse sinus. These clots, situated above the tentorium, showed the signs of a hæmorrhage from the middle meningeal artery.*

Conclusions

Reviewing the cases of the literature and my own, we can draw some important conclusions. *First*, that isolated extradural cerebellar hæmatoma are apparently always due to a laceration of the transverse sinus or one of the tributary veins. Duret stated that rupture of the posterior meningeal artery could produce a cerebellar hæmatoma, but this, of course, is not true. Coleman and Thomson believe that a hæmatoma of the posterior fossa does not occur without skull fracture. My own case showed a separation of the left part of the lambdoid suture, a condition in its kind and effect not much different from a fracture. It is, however, important to note that a fracture can be invisible in the X-ray pictures, as in McKenzie's case.

The *second* conclusion is the fact, underlined by Coleman and Thomson, that owing to the relatively low pressure within the transverse sinus the development of a cerebellar hæmatoma may take rather a long time. More than 60 hours passed in Coleman's case before drowsiness as the first clinical symptom appeared; 30 hours elapsed in my case before the first fit occurred. In McKenzie's case there was a lucid interval of 30 hours' duration, but during this time hypotonia of the limbs was found.

It is doubtful if the few clinically observed cases permit a certain syndrome of cerebellar hæmatoma to be established.

Coleman and Thomson describe the diagnostic criteria for recognition of an extradural hæmorrhage in the posterior fossa as follows: History of a blow on the back of the head severe enough to produce a fracture of the skull, with or without unconsciousness; gradually increasing headache, usually accompanied by nausea and vomiting; progressive drowsiness and restlessness; forced position of the head; neck stiffness; nystagmus (which may be absent); disappearance of deep reflexes; hypotonia; when the drowsiness changes into unconsciousness, pulse and respiration become irregular, and death is imminent.

The symptomatology and the course of McKenzie's case and my own were, however, somewhat different from this description. It is certainly of importance that " cerebellar fits " can be the outstanding feature of the clinical picture. In such a case the diagnostic problem is not a difficult one; if no fits occur, as in Coleman and Thomson's case, certainly only repeated neurological examination and careful observation will deliver early enough conclusive symptoms for a correct diagnosis.

The *prognosis* in a case of ruptured sinus is necessarily bad. Of 42 cases with and without fracture of the skull found in the literature and reported by Ricard (1929) one-half died. Nine patients in this series had no fracture of the skull; they all died, and the diagnosis was established only at the post-mortem examination. Only the very clear symptoms of the case above reported saved her from death.

Summary

What appears to be the first case of extradural cerebellar hæmatoma successfully operated upon is described and discussed. The literature relative to the subject is discussed.

* While this paper was in the press, Gurdijan and Webster published a case of extradural hæmatoma over the cerebellum and occipital lobes due to a penetrating wound of the skull; the patient was operated upon and cured. *Surg. Gynec. Obstet.*, 75, *Internat. Abstracts*, 206.

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PROCAINE NERVE BLOCK IN THE INVESTIGATION OF PERIPHERAL NERVE INJURIES *

BY

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(RECEIVED 1ST AUGUST, 1942)

DURING the past two years at the Oxford Peripheral Nerve Injury Centre I have found that a great deal of information may be gained by the simple[1] procedure of anæsthetizing peripheral nerves with procaine. The procedure is not original—it has been employed by J. C. White in the investigation of peripheral vascular disorders, and by Woollard in the investigation of sensory dissociation. I have employed nerve blocks in over fifty cases and have succeeded in establishing a satisfactory technique. In no case has there been evidence that the procedure is harmful.

Nerve block has been used in the following investigations:

1. Anomalous innervation of muscles.
2. " Supplementary " and Trick movements.
3. Sensory and sudomotor distribution of peripheral nerves, in relation to the differentiation of complete and incomplete or recovering lesions.
4. The vasomotor distribution of peripheral nerves.

Technique.—I have tried out several methods of injection and have now found a reliable method by means of which any nerve can be readily anæsthetized for a period of from three to four hours—a time sufficient for the completion of all necessary investigations. Originally I employed various strengths of procaine without adrenalin, but soon found that the block induced was of insufficient duration. Five per cent. procaine was especially unsatisfactory because several patients complained of considerable pain when the effects of injection wore off. I now employ a 2 per cent. solution of procaine containing adrenalin at a strength of 1 in 50,000.

If possible the nerve to be blocked is identified by palpation. This is possible in the case of the ulnar above the medial epicondyle and in the radial at the level of mid-arm and the lateral popliteal at the neck of the fibula. In the case of small cutaneous nerves such as the medial or lateral cutaneous nerves of the forearm, the superficial radial or the sural nerve the course of the nerve may be mapped out by percutaneous unipolar faradic stimulation. In the case of deeply placed impalpable nerves such as the median or medial popliteal the surface marking is outlined and an attempt is made to locate the nerve with the exploring needle passed through the skin.

In all cases I employ the apparatus shown in Fig. 1. This apparatus is designed for direct unipolar stimulation of the nerve to be injected. The outside of the needle is coated with a phenyl resin which insulates all but 1 or 2 mm. at the tip. The needle is attached to a record syringe containing 2 per cent. procaine with 1/50,000 adrenalin. To the metallic part of the lower end of the barrel is attached a small metal clip and a length of insulated wire nine inches in length. This clip and its attached wire are sterile. To the end of this wire is clipped an unsterile cable leading to one terminal of an ordinary faradic coil. The other terminal leads off to a broad moist plate applied to some neutral area such as the back of the thigh. Thus when the apparatus is connected only the tip of the exploring needle acts as a stimulator, and as soon as the nerve is touched the patient experiences a tingling over the peripheral distribution of the nerve. It may be noted that in normal nerves only a very weak stimulus is tolerated. Excessive stimulation causes severe pain. Only the finest hypodermic needles are employed. I have seen no ill effects from the injection, but it is conceivable that if a large needle were used some intraneural vessels might be damaged and the intraneural hæmorrhage lead to permanent damage.

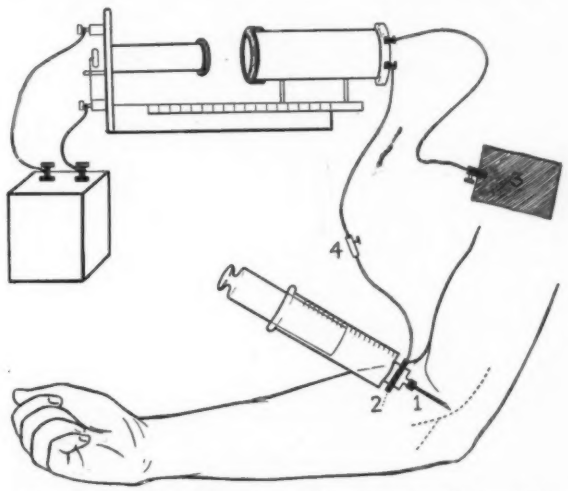

FIG. 1.—1. Hypodermic needle coated with insulating phenyl resin except at the extreme tip. 2. Clip attached to the metallic base of the syringe. The needle, syringe, clip and the attached lead are sterile. 3. Neutral plate usually applied to the thigh. 4. Connection between sterile and unsterile lead.

In the case of the ulnar, radial and lateral popliteal nerves an intraneural injection may be made and only 2 c.c. of solution is necessary for complete anæsthetization. In other nerves intraneural injection is rarely possible. The solution is injected around the nerve and 5 to 10 c.c. may be necessary for complete anæsthetization. If carried out slowly and carefully the injection rarely gives rise to more than a momentary slight pain. After the injection the needle is left in place. If the block is successful one finds that within a few minutes the faradic stimulus may be greatly increased without

* A section of the Jacksonian Prize Essay, 1941.

causing pain. It is essential to use as small a quantity of solution as possible and to block the nerve at a site remote from other main nerve trunks. If large quantities are injected the solution may diffuse and block nerves some distance from the site of injection. For instance, if the technique of injection is faulty it is possible to block the medial cutaneous nerve of the arm in the course of ulnar block at the elbow, and in the course of median block at the wrist the ulnar nerve may be affected. Indeed median nerve block at the wrist is extremely difficult on account of this possibility of spread to the ulnar.

Criteria of Completeness of Nerve Block

The order of loss of function after procaine block is well established (Gasser and Erlanger, 1929) and I have nothing to add to what is already known. The effects are peripheral vasodilatation, loss of sweating, hypoalgesia, and lastly complete analgesia and anæsthesia and motor paralysis. If the injection is sub-epineural the effects appear within a minute or two, but if the solution is merely diffused about the nerve, the effects appear gradually and complete anæsthetization may take 10 to 15 minutes. When adrenalin is employed the effects persist from 3 to 4 hours.

Before a nerve block is regarded as complete, all of the following conditions must be fulfilled:

1. Full vasodilatation
2. Anhidrosis
3. Anæsthesia and analgesia

(1, 2, 3: in the autonomous zone of the nerve.)

4. Complete and lasting paralysis of muscles supplied by the nerve distal to the site of block.

Investigation of anomalous innervation of muscles

In a previous paper (Guttman and Highet 1942), I have discussed the innervation of the muscles of the thenar eminence. In many cases of injury to the median nerve one or another of the thenar muscles which, according to the classical description, are innervated by the median, may remain unparalysed, and so give rise to uncertainty in diagnosis. Is the median lesion incomplete or has the muscle an anomalous ulnar innervation? Fig. 2 shows attempted opposition in a case where flexor brevis pollicis and probably part of opponens pollicis were active. The correct diagnosis was readily established by means of procaine block of the ulnar nerve at the elbow. All activity in the thenar muscles was abolished.

FIG. 2.

FIG. 3.

Fig. 3 shows attempted opposition after ulnar nerve block. Later at operative exploration the median nerve was found completely divided.

The innervation of flexor profundus digitorum is subject to considerable variation. Usually the slips of the muscle to the 2nd and 3rd digits are innervated by the median and the slips to the 4th and 5th by the ulnar. The slips to the 3rd and 4th digits frequently receive a double innervation. In some cases the slip to the 5th digit may also receive a median innervation. We have not yet seen a case in which the slip to index was innervated by the ulnar nerve.

In Fig 20 flexion of the fingers is shown in a case of injury to the ulnar nerve above the level of the elbow. There was complete motor paralysis (including flexor carpi ulnaris) with the exception that

flexor profundus digitorum to the 4th digit was normal and that to the 5th digit only slightly weaker than normal. In addition, as will be mentioned later, the area of sensory loss was unusually small. In this case the median innervation of flexor profundus to the 4th and 5th digits was established by nerve block. First the ulnar nerve was blocked immediately above the level of the lesion. The block was almost certainly complete because the unipolar stimulating needle was employed and after the injection no pain could be aroused by faradic stimulation. The function of the long flexors remained unaltered. However, there is a real difficulty in this connection. After block of an injured nerve what means has one of assessing the completeness of the block? Failure to arouse pain by direct stimulation is an insufficient criterion because although the pain fibres are anæsthetized the motor fibres may still be unaffected. Nevertheless in this case strong stimulation by means of the exploring needle failed to bring about any contraction in flexor profundus.

Secondly, a few days later the median nerve was blocked in the antecubital fossa. The block was complete according to the four criteria mentioned above. This block was conclusive for flexor profundus digitorum was completely paralysed (Fig. 23). Subsequent operative exploration confirmed the completeness of the injury to the ulnar nerve.

Investigation of " Supplementary " and " Trick " Movements

Excluding anomalous and double innervation of muscles as a source of " trick " movements there are two classes of so-called " trick " movements which deserve separate description. " Supplementary " movements at a joint are performed by the contraction of muscles which are able to take over the function of the paralysed muscles. Most of these supplementary actions are well known. For instance, abductor pollicis longus can flex the wrist in cases of complete ulnar and median paralysis. The common flexor group of muscles, chiefly pronator teres and flexor carpi radialis, can sometimes flex the elbow when biceps, brachialis and brachio-radialis are paralysed. It is inaccurate to include such supplementary movements under the general term " trick " movements. Supplementary movements are to be encouraged as much as possible, and the patient should never be told they are tricks. The term " trick movement " should be reserved for movement where the examiner may be " tricked " by his faulty method of examination. True trick movements are all passive movements and are brought about by three agencies (Wood-Jones, 1921). 1. Tension on paralysed muscles by the overaction of their antagonists. 2. " Rebound " movements. 3. The action of gravity. I am not concerned here with true trick movements but with supplementary movements. By means of peripheral nerve block it is possible to identify the muscle or muscles which are responsible for the supplementary movement. In most cases of course the identity of the muscle is obvious, but in certain cases nerve block is of value.

I have encountered several cases of complete paralysis of the deltoid muscle where full active abduction of the shoulder was possible. The four main muscles responsible for abduction at the shoulder are the deltoid, supraspinatus, trapezius, and serratus anterior. Paralysis of any one muscle affects abduction. When deltoid and supraspinatus are both paralysed there is no active abduction at the scapulo-humeral joint. When deltoid alone is paralysed full abduction may be possible. One would assume that this is due to the supplementary action of supraspinatus, but it has been suggested that the long head of biceps is capable of carrying out supplementary abduction. That the supplementary abduction is due to supraspinatus may be readily demonstrated by nerve block of the suprascapular nerve at the level of the suprascapular notch of the scapula. This nerve block is rather difficult, but I have been successful on five occasions and have produced complete paralysis of supraspinatus and infraspinatus. Fig. 4 illustrates full active abduction of the shoulder in a case of complete paralysis of the deltoid. Fig. 5 shows that abduction at the scapulo-humeral joint has been abolished by paralysis of supraspinatus after blocking the suprascapular nerve.

In several cases of complete radial paralysis I have observed active extension of the terminal phalanx of the thumb. This was a true supplementary movement for the thumb was held in such a position that " trick " extension by passive tension on extensor longus pollicis was prevented. Sometimes a slip of abductor brevis pollicis gains insertion into the radial side of the tendon of extensor longus pollicis. I was able to demonstrate by median nerve block that when the abductor brevis pollicis was paralysed active extension of the terminal phalanx was no longer possible.

Investigation of Sensory and Sudomotor Distribution of Peripheral Nerves

The area of skin supplied exclusively by one nerve is referred to as the autonomous zone of sensory distribution. In this zone all modalities of cutaneous sensibility are lost after nerve section. However, this autonomous zone does not represent the total area of distribution, for if all neighbouring nerves are divided and the nerve in question left intact the area of distribution will be found to be much more extensive than the autonomous zone, and this residual area is referred to as the maximal zone. The difference in size between the autonomous and maximal zones is due to nerve overlap. From macroscopic dissection it is impossible to attain an adequate insight into the distribution of cutaneous nerves. The autonomous zone of a sensory nerve is invariably of less extent than its anatomical distribution. Furthermore, there are considerable variations in the distribution of sensory nerves, both in different individuals and in the same individual on right and left sides. The difference in the size of the autonomous and maxima

zones of any given nerve in any given patient may readily be demonstrated by means of peripheral nerve block. Another source of difficulty is that after nerve section the area of sensory loss tends to undergo progressive shrinkage especially in the first few weeks after section. This shrinkage is due to nerve overlap and concerns chiefly the nerve fibres subserving touch (Pollock, 1920; Weddell, Guttmann and Gutmann, 1941).

The clinical problems may be stated as follows:

1. When a nerve is injured and the area of sensory loss is anomalous one may be uncertain whether the lesion is complete or partial.
2. When the area of sensory loss undergoes shrinkage one may be uncertain whether this shrinkage is due merely to overlap or to regeneration in the injured nerve.

Both problems may be solved by peripheral nerve block.

There are two methods available. First, the affected nerve may be blocked immediately above or below the site of injury. This method is open to the serious objection that there are no adequate criteria of the completeness of the block. Secondly, the neighbouring nerves may be blocked. This is the better method, since one can be certain of the completeness of the block.

Illustrative Cases

The following cases illustrate the usefulness of nerve block. In the photographs the area of sweating is black and areas of hypohidrosis show fine black pin-points of sweating. The border of anæsthesia to a 1 gram. von Frey hair is represented by a continuous line, the border of anæsthesia to cotton wool by a notched line. The border of analgesia to superficial needle prick is represented by black dots, so that pain sensibility is present wherever dots are marked within the touch line. The crosses represent the presence of pain sensibility to slightly deeper needle pricks (deep cutaneous pain) (Guttmann and Highet, 1942).

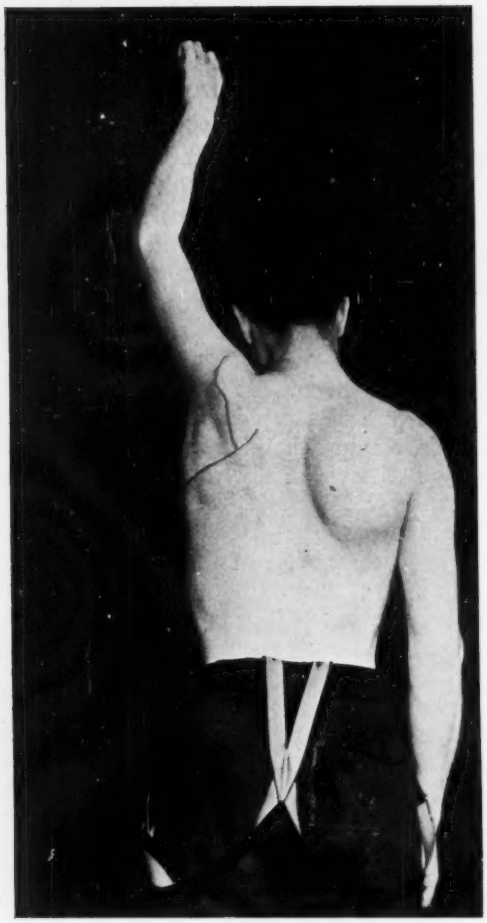

FIG. 4.

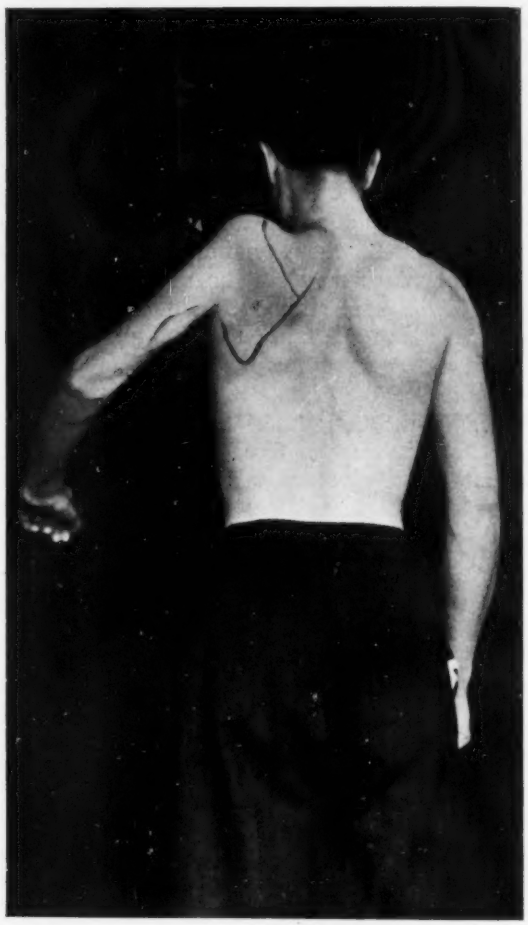

FIG. 5.

Case 1.—Figs. 6 to 16 illustrate a series of nerve blocks in a patient in whom complete division of the median nerve was established by nerve blocks and later confirmed by operative exploration. The nerve blocks were performed when the case was referred to us five months after the nerve injury and operative exploration was performed within a few weeks of the investigation.

The diagnosis in this case was very difficult because all thenar muscles were innervated by the ulnar nerve (Fig. 6). Figs. 7 and 8 show the autonomous zone of

FIG. 6.

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 10.

FIG. 11.

FIG. 12.

FIG. 13.

sensory loss and loss of sweating. There is considerable overlap into the median area by both ulnar and radial nerves. Thus there is a complete band of pain sensibility over the metacarpo-phalangeal joints of the 1st, 2nd and 3rd digits and another band across the centre of the palm. There is no loss of sensibility or sweating on the 4th digit. Fig. 9 shows the complete paralysis of the thenar muscles (photographs during attempted opposition) after nerve block of the ulnar at the level of the medial epicondyle. Figs. 10 and 11 show the distribution of loss of sensation and sweating. The picture now represents a combined median and ulnar paralysis. The ulnar overlap is obliterated but the radial overlap is still evident over the metacarpo-phalangeal joints of the 1st and 2nd digits. This picture illustrates the maximal overlap by the radial nerve. Figs. 12 and 13 show the distribution of loss of sensation and sweating after nerve block of the radial (superficial radial nerve in the lower third of the forearm). The overlap of the radial nerve into the median area has been obliterated and the maximal overlap by the ulnar is shown. For instance, touch sensibility on the ulnar side of the 3rd digit is subserved by the ulnar. If Figs. 10 and 12 were superposed the resulting picture would be Fig. 7. It may be noted that in Fig. 12 in spite of radial nerve block the lateral side of the thenar eminence has retained some touch and pain sensibility and slight sweating. This is due to overlap by the lateral cutaneous nerve of the forearm. Figs. 14, 15, and 16 show the distribution of loss of sensibility and sweating after nerve block of the lateral cutaneous nerve of the forearm (the site of block is marked by an arrow). In this series of pictures the whole area of median loss was not outlined, but only the margin of the area on the thenar eminence. Figs. 12 and 16 illustrate the overlap by the superficial radial and lateral cutaneous nerves of the forearm. Blocking of either nerve alone failed to abolish all sensibility and sweating over the lateral part of the thenar eminence which shows that this area was supplied by both nerves.

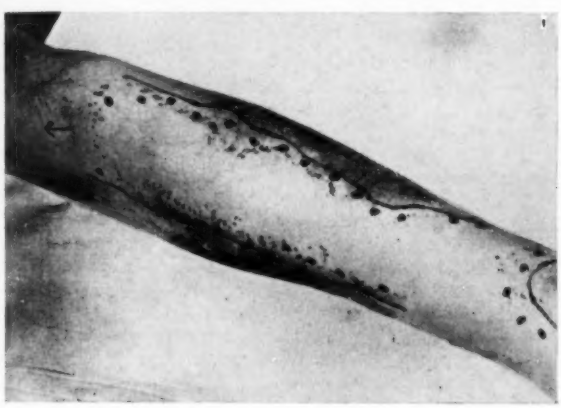

FIG. 14.

Case 2.—A case of injury to the median nerve at the wrist in which complete division was confirmed by operative exploration after the diagnosis had been established by nerve block. The nerve blocks were carried out when the patient was referred to us five months after the injury. In this case flexor brevis pollicis was active and innervated by the ulnar nerve. Fig. 17 shows the area of sensory loss. The area of anæsthesia and analgesia is rather small but outside the line of anæsthesia is a zone of hypoæsthesia (notched line). There is some touch and pain sensibility on the ulnar side of the 3rd digit and a band of pain sensibility across the base of the 2nd digit and over the proximal phalanx of the thumb. Figs. 18 and 19 show the loss of sensibility and sweating after nerve block of the ulnar and radial nerves at the same session. The ulnar was blocked at the level of the medial epicondyle and the radial at the level of the spiral groove of the humerus. The picture represents a combined median, ulnar and radial paralysis. It is obvious that the median lesion is complete, for there is now no sensation or sweating in the median area. Fig. 18 illustrates slight overlap onto the proximal part of the palm by one of the forearm nerves probably due to the medial cutaneous nerve of the forearm, but no attempt was made to prove this. Also Fig. 19 shows the overlap by the lateral cutaneous nerve of the forearm

FIG. 15.

FIG. 16.

onto the metacarpal and dorsum of the proximal phalanx of the thumb.

Case 3.—This was a case of complete division of the ulnar nerve above the medial epicondyle, later proved by operative exploration. The nerve blocks were performed when the patient was referred to us 5 months after the injury.

Fig. 20 illustrates the action of flexor profundus digitorum to the 4th and 5th digits (referred to on page 102). Figs. 21 and 22 illustrate the loss of sensibility and sweating. The autonomous zone of the ulnar is unusually small and includes only the extreme tip of the 5th digit, the ulnar side and dorsum of the 5th digit and the ulnar side of the dorsum of the hand. The ulnar nerve was blocked a few centimetres above the level of the lesion. The sweating an sensory tests yielded findings identical with those shown in Figs. 20, 21, and 22. A few days later the median nerve was blocked in the antecubital fossa. The findings are shown in Figs. 23 and 24. There is now complete median and ulnar paralysis. The maximal zone of the radial nerve is illustrated on the dorsum of the hand. Fig. 23 also illustrates the obliteration of all action in flexor profundus digitorum. This nerve block confirmed the previous ulnar block and showed that the ulnar lesion was complete and that the small area of sensory loss and anhidrosis was due to extensive overlap by the median nerve.

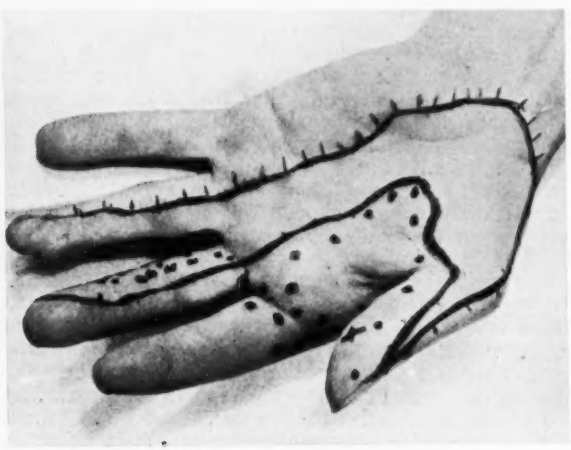

FIG. 17.

Case 4.—This man sustained a traction injury of the upper trunk of the brachial plaxus—the injured segment was excised and a nerve graft inserted. The whole superficial radial nerve was excised for use as a graft.

Fig. 25 shows the loss of sensibility and sweating on the dorsum of the hand 3 weeks after operation. We were interested in the large tongue of sensibility and sweating extending from the dorsum of the forearm and into the superficial radial area. We thought it probable that this tongue was an extension of the dorsal cutaneous nerve of the forearm. Accordingly the radial nerve was blocked at the level of the spiral groove of the humerus just above the origin from the radial nerve of the dorsal cutaneous nerve of the forearm. Fig. 26 illustrates the area of loss of sweating and sensation after nerve block and shows that our surmise was correct.

Case 5.—This was a case of injury to the lateral popliteal nerve at the level of the knee. The area of loss of sensibility and sweating was typical except that there was a band of pain sensibility (marked by crosses) over the front of the leg just above the ankle and the area of loss on the dorsum of the foot was unusually narrow with an almost complete bridge of pain sensibility in the middle of the area, see Figs. 27 and 28. Nerve block of the lateral popliteal nerve was performed at the level of the neck of the fibula. The sensory and sweating pictures after nerve block were identical with the previous pictures. Thus the band of pain sensibility over the front of the leg was due to overlap by the saphenous and sural nerves and the small area of sensory loss on the dorsum of the foot to overlap by the sural and medial plantar nerves. Complete division of the lateral popliteal nerve was confirmed by operative exploration.

Case 6.—In this case the ulnar and radial nerves were blocked, the ulnar at the level of the medial epicondyle and the radial at the level of the spiral groove of the humerus.

FIG. 18.

FIG. 19.

FIG. 20.

FIG. 21.

FIG. 22.

FIG. 23.

FIG. 24.

FIG. 25.

FIG. 26.

FIG. 27.

Fig. 29 illustrates the maximal zone of the lateral cutaneous nerve of the forearm extending into the first interosseous space, the area which most text-books figure as innervated by the radial nerve. In this figure pain sensibility is not outlined. Fig. 30 illustrates the overlap by the lateral cutaneous nerve of the forearm into the superficial radial area in another case where both ulnar and radial nerves were blocked for another purpose.

Case 7.—In this case nerve blocks were carried out to differentiate true recovery from shrinkage by overlap.

FIG. 28.

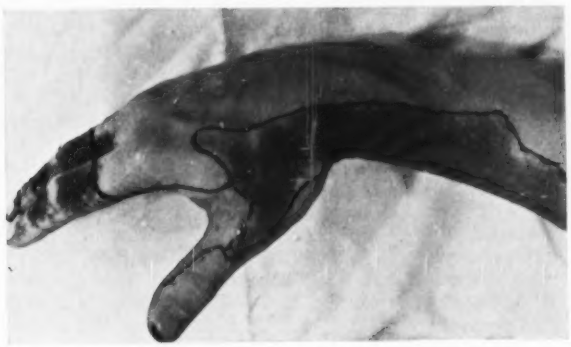

FIG. 29.

FIG. 30.

FIG. 31.

FIG. 32.

Fig. 31 illustrates the area of sensory loss on 24/3/41, five months after division of the median nerve at the wrist (28/12/40). Fig. 32 illustrates the area of loss of sensibility and sweating five months after suture of the median (11/9/41). There were fine pin-points of sweating over the median area in the palm and deep cutaneous pain was present, but not superficial cutaneous pain. We were uncertain whether this return of pain sensibility represented true recovery or shrinkage by overlap. Accordingly the ulnar and radial nerves were blocked at the one session. Fig. 33 illustrates the area of true recovery of pain sensibility in the median area (13/9/41). For clearness the pain dots have been joined up to enclose the area of recovery.

Case 8.—This case illustrates the use of nerve block in the differentiation of true regeneration from shrinkage by overlap of neighbouring nerves. This was a case of complete division of the median and ulnar nerves in the mid arm. Suture had been performed elsewhere. Figs. 34 and 35 illustrate the disturbance of sweating and sensibility on 6/5/41. Fig. 36 shows the presence of some deep cutaneous pain (crosses) extending into the median area over the thenar eminence and radial side of the palm (17/7/41). Fig. 37 shows an advance of pain sensibility, chiefly deep cutaneous pain (2/2/42), beyond that shown in Fig. 36. We were uncertain whether this was due to true regeneration or to overlap by the adjacent radial nerve. Fig. 38 illustrates the condition after nerve block of the radial nerve at the level of spiral groove of the humerus. The pain sensibility over the radial side of the palm and over the thumb is still present and represents recovery in the median nerve and as the measure shows, an advance of 13 cm. distal to the wrist.

It is noteworthy that recovery has taken place chiefly in the part of the median area adjoining the area supplied by the intact radial nerve.

Case 9.—This was a case of injury to the median nerve. He was referred to us 18 months after the injury. The area of sensory loss is illustrated in the right-hand part

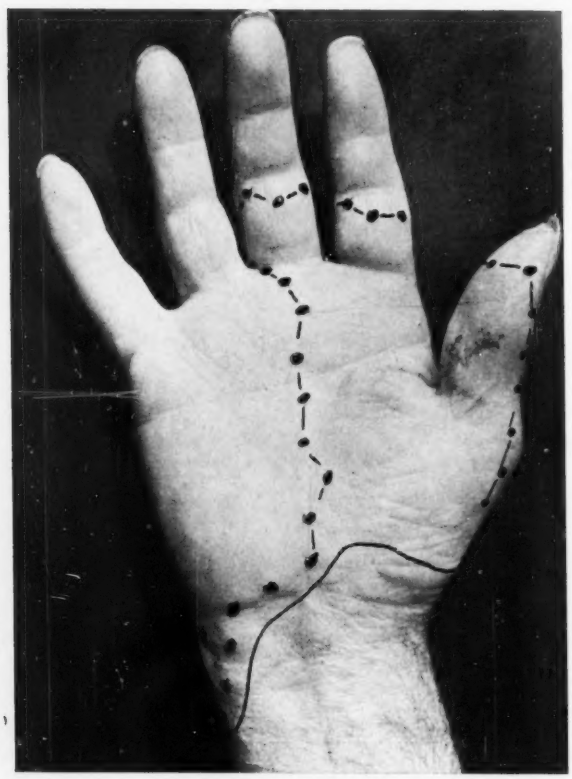

FIG. 33.

FIG. 34.

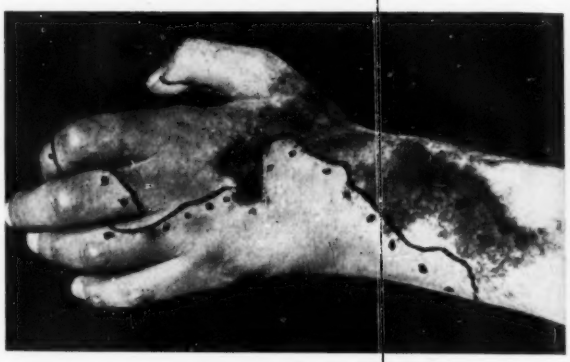

FIG. 35.

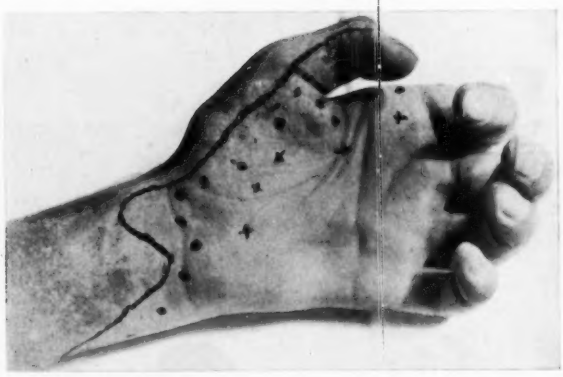

FIG. 36.

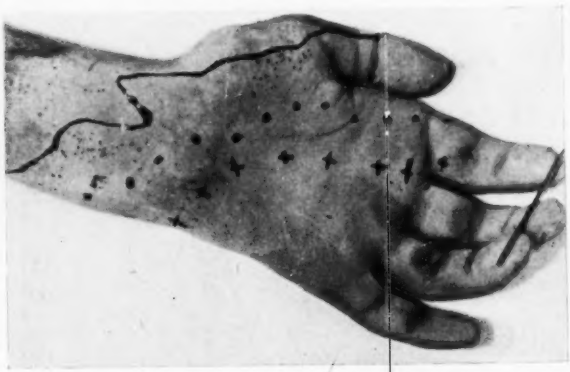

FIG. 37.

of Fig. 39. There was complete analgesia of the tip of the thumb and the whole of the index finger, but no analgesia on the middle finger or over the palm. Anæsthesia was confined to the radial 2½ digits. The problem in this case was whether this sensory loss indicated a small autonomous zone after complete division of the median or a sensory loss due to incomplete division of the median. Accordingly the ulnar nerve was blocked at the level of the medial epicondyle. The resulting sensory loss of ulnar distribution is illustrated in Fig. 39. There was a broad band of touch and pain sensibility between the median and ulnar areas. The nerve block indicated that the median lesion was incomplete.

To confirm this a second nerve block was performed 2 days later. The median nerve was blocked. Fig. 40 shows the area of anæsthesia and analgesia thus obtained. The area of median sensory loss now involves the classical area.

At operative exploration a few days later incomplete division of the median nerve was disclosed. There was a well-marked lateral neuroma at the site of injury.

Case 10.—This was a case of injury to the median and radial nerves in the axilla. Fig. 41 illustrates the area of loss of sensibility and sweating in the hand. The area of analgesia on the front of the hand is unusually small and analgesia is limited to the index finger and thumb. As in Case 9 the question arose whether this was a case of complete or incomplete division of the median. Accordingly ulnar nerve block was performed at the level of the medial epicondyle. Fig. 42 shows the result of a sweating and sensory test after the nerve block. All sweating and sensibility has been abolished in the hand. Thus the small area of median sensory loss in Fig. 41 is due to extensive overlap into the median area by the ulnar nerve. At operative exploration the median nerve was found completely divided.

Case 11.—This case illustrates the value of nerve block in the investigation of dissociated paralysis. This was a case of transient block of the radial nerve due to crutch palsy. When he was referred to us five days after the onset of the paralysis there was complete paralysis of all

FIG. 38.

FIG. 39.

FIG. 40.

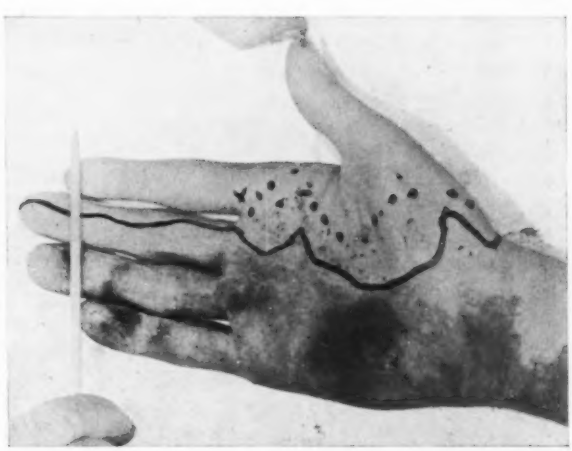

FIG. 41.

muscles of radial innervation, including triceps. As in all cases of transient block the muscles retained their faradic excitability. There was no loss of sensibility or sweating. Neurapraxia is one type of dissociated paralysis in which, though there is complete loss of voluntary power in the muscles supplied by the injured nerve, there is usually very slight or no detectable disturbance of sensibility and sweating. To prove that this was a case of dissociated paralysis the radial nerve was blocked at the level of the spiral groove of the humerus. The sweating and sensory tests shown in Fig. 43 show that there is now loss of sensibility and sweating over the whole distribution of the radial nerve, the areas supplied by the lower lateral cutaneous nerve of the arm, the dorsal cutaneous nerve of the forearm and the superficial radial.

Case 12.—This case illustrates the shrinkage of the area of sensory loss by overlap of neighbouring nerves. In this case I produced an experimental lesion in continuity of the lateral cutaneous nerve of the thigh in a volunteer. Accurate sensory and sweating tests were performed at frequent intervals in order to investigate the process of sensory regeneration. Full details of the investigation are to be published at a later date.

On 14/3/41 the lateral cutaneous nerve of the thigh was exposed under local anæsthesia and forcibly crushed with artery forceps. Complete axonotmesis was produced at a level just below the anterior superior iliac spine. Fig. 44 shows the area of loss of sensibility and sweating on 3/4/41. Only the lower part of the area is shown in this and in the subsequent pictures. The noteworthy feature is the small size of the intermediate zone. Unfortunately nerve block was not performed before operation, but Fig. 45 illustrates the area of loss of sensation and sweating after nerve block of the corresponding nerve of the opposite leg. As in Fig. 44 the intermediate zone is of very small extent. Fig. 46 shows the sensory and sweating disturbance on 6/6/41 before any true regeneration was possible to this level. The intermediate zone shows a considerable enlargement. Sweating and pain sensibility now extend well within the touch line.

On 8/5/42 pain sensibility had recovered over the whole area and there was also some sweating over the whole area. Nerve block was performed and was certainly complete. Fig. 47 shows the area of loss of sweating and sensibility after nerve block. The intermediate zone is larger than in Figs. 44 and 45.

This nerve block shows that after recovery took place in the injured nerve the hyperactivity of the neighbouring nerves was still evident—in other words, that the signs of shrinkage by overlap from neighbouring nerves were still present.

I have noted repeatedly that the area of sensory loss and anhidrosis after nerve block of normal nerves is usually more extensive than the corresponding area encountered in cases of complete division of peripheral nerves. I believe that Case 12 reveals the cause of this discrepancy.

Cases of peripheral nerve injury are almost invariably referred to this centre several months after the original injury. By this time shrinkage by overlap has already taken place so that the area is less extensive than immediately after the injury. However, in several cases to be reported elsewhere (Guttmann and Highet, 1942) we have been sufficiently fortunate to be able to carry out detailed examinations immediately after the injury and have demonstrated a progressive shrinkage of the area of sensory loss by nerve overlap at a time when there was no possibility of true recovery by regeneration.

The above cases, however, illustrate the difficulty in making a clinical distinction between shrinkage by overlap and the early stages of true regeneration.

Investigation of the Vasomotor Distribution of Peripheral Nerves

When a peripheral nerve containing sensory fibres is completely anæsthetized full vasodilatation occurs in the area of skin supplied by it. In the course of various planocaine nerve blocks I have made recordings of skin temperature with thermocouples. The investigation of vasomotor paralysis in injured nerves is not yet completed, but my impression is that the distribution of vasomotor fibres is identical with the distribution of unmyelinated fibres subserving sweating and pain. In this connection I have investigated only the median, ulnar, and radial nerves. After nerve block of normal nerves full vasodilatation takes place over the 5th digit and almost full vasodilatation over the 4th digit. After nerve block of injured nerves vasodilatation takes place only in the areas which have preserved some sweating and pain sensibility. Also in recovering nerve lesions vasodilatation takes place only in the areas which have recovered sweating and pain sensibility.

Sympathetic Nerve Block in the Investigation of Causalgia

There is a growing tendency to refer causalgic pain to some disturbance of the peripheral sympathetic system. The following case illustrates the use of sympathetic block in this connection.

Case 13.—On 26/8/40 a woman aged 27 sustained a bomb splinter injury of the left thigh. A fragment injured the sciatic nerve in the mid thigh. For a few days only there was a sciatic paralysis. Within half an hour of the injury she complained of severe burning pain over the whole foot. The pain was accompanied by increased sweating in the foot and by severe emotional disturbance. On 12/11/40 peri-arterial sympathectomy was performed at another hospital. The femoral artery was exposed in Hunter's canal and the adventitis injected with absolute alcohol. This operation had no effect on the pain. On 17/7/41 she was admitted to the Wingfield-Morris Orthopædic Hospital. There was no motor paralysis or sensory loss, but the whole sole and part of the dorsum of the foot showed marked over-response to tactile and painful stimuli. She still complained of spontaneous burning pain and was unable to walk on account of the tenderness of the sole of the foot. The skin temperature of the whole of the left foot was increased 3° C. as compared with the normal foot.

On 29/7/41 the left lumbar sympathetic chain was infiltrated with 30 c.c. 1·5 per cent. procaine with 1/30,000 adrenalin. At the time of the injection the patient was weeping and miserable. Within 10 minutes of the injection she sat up and smiled and volunteered the information that her pain had completely disappeared and that the foot had never been so comfortable. Temperature recordings showed full vasodilatation of the left foot. Two hours after the injection the pain returned and within four hours of the injection had reached its former intensity.

On 30/7/41 neurolysis of the sciatic nerve was performed. There was a band of scar encircling the nerve at the level of the mid thigh but the nerve itself appeared normal except for a slight area of induration of the medial popliteal component. This operation had no effect on her pain, in fact, the pain and over-response to stimuli showed a marked increase.

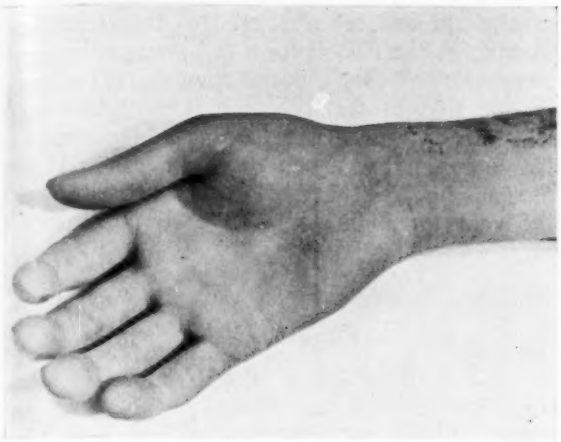

FIG. 42.

FIG. 43.

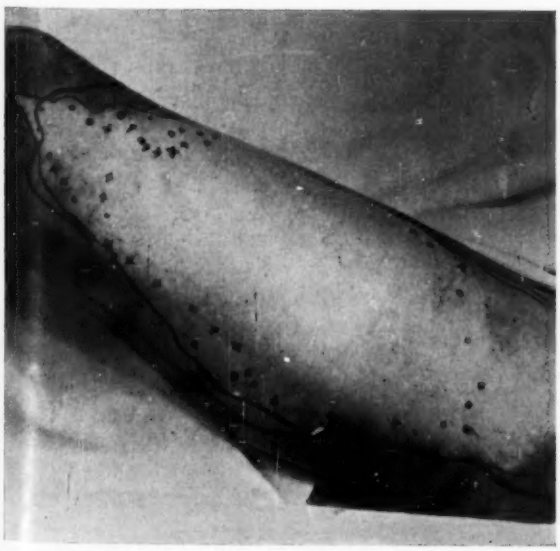

FIG. 44.

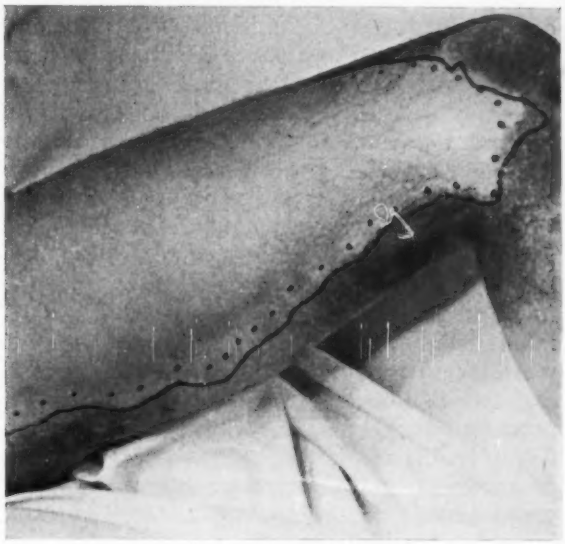

FIG. 45.

FIG. 46.

FIG. 47.

Before proceeding to lumbar sympathectomy certain controlled observations were made. An attempt was made to produce full vasodilatation of the legs by immersion of the arms and upper part of the trunk in a hot-air chamber—the legs were left exposed to the room temperature. Reflex vasodilatation occurred in both feet, but the pain in the left foot rapidly became intolerable. In other words, reflex vasodilatation, far from relieving the pain, seemed only to increase it. On 14/9/41 the left lumbar sympathetic chain was again subjected to paravertebral injection. The chain was first infiltrated with normal saline. This had no effect whatever on her pain. The needle was left in situ and twenty minutes later 30 c.c. of 1 per cent. procaine was injected. As on the previous occasion (29/7/41) all pain disappeared within 10 minutes of injection. Temperature recordings showed full vasodilatation of the left foot. On 17/9/41 left lumbar sympathectomy was performed with removal of the 2nd, 3rd, and 4th lumbar ganglia and the intervening sympathetic chain.

Since operation she has had immediate and complete relief of pain, and she walks normally and suffers no disability. All hyperæsthesia and hyperalgesia has disappeared. She was last observed on 8/6/42.

It is very difficult to assess the effect of any operative procedure directed to the relief of causalgia, for all symptoms are subjective and spontaneous recovery is not uncommon. However, I believe that in this case the investigation was carried out with sufficient controls to warrant a belief that lumbar sympathectomy relieved the causalgia. I believe that in all such cases sympathetic nerve block should be employed before operation.

Conclusions

Peripheral nerve block affords a very useful method of study of the function of peripheral nerves. Anatomical descriptions of the distribution of peripheral nerves should be based on data obtained by this technique as well as on data from cases of division. The method may be applied clinically in the differentiation of complete from partial and recovering lesions of peripheral nerves. The method is not harmful, and if the technique is satisfactory it is an extremely useful diagnostic procedure.

I am grateful to Dr. Feinstein of the Department of Human Anatomy, Oxford, for preparing for me needles insulated with phenyl resin.

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FACTORS AFFECTING RECOVERY OF SENSORY FUNCTION AFTER NERVE LESIONS

BY

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(RECEIVED 7TH AUGUST, 1942)

MOST of our knowledge of the processes of sensory recovery after nerve lesions is derived from human cases. Indeed, in some ways man is most suitable for such work, because he can give verbal information about the quality of sensation which is felt. But there are many problems which can only be solved by the comparison of recovery under conditions which differ in respect of one variable only, say level of lesion. Human cases are rarely sufficiently comparable to allow this to be done. Complications are introduced by such factors as varying length of nerve that has been crushed, the time between injury and operation, skill of the surgeon, and so on.

It is somewhat surprising, therefore, that there has been remarkably little detailed study of sensory recovery in animals. Vanlair (1882 and 1887) studied recovery of sensation on the sole of dogs after various operative procedures, and several workers have used sensory recovery among other signs for testing the suitability of surgical procedures (Takimoto 1917, Huber 1919, Gosset and Bertrand 1938, Tangari 1940, Muesch and Roessel 1941). Most of the observations on recovery of sensation following the interruption of a nerve in animals are restricted to a brief statement that recovery of sensation had taken place after a certain time. Such statements are both insufficient and unsatisfactory. It will be seen later that recovery of sensation in a denervated area is a complex process and only a part of it is due to regeneration of the interrupted nerve. An exact description of the denervated area in which recovery is observed is thus necessary before any conclusions may be drawn. Therefore a clear knowledge of the sensory distribution of various nerves is an essential preliminary to the study of recovery of sensation in animals. In rabbits there is no satisfactory account of the areas innervated by the various peripheral nerves. No doubt the reason for this lack of investigation has been the fear that reflex responses of the animal would not be sufficiently consistent to enable accurate mapping of the sensory state of the skin. However, if properly handled, rabbits may serve as satisfactory "observers." The responses which may be most conveniently used in the rabbit are withdrawal reactions to pin prick stimuli.

The work reported here may be said to have three objects: first, to delimit the maximal and autonomous areas of the skin served by various nerves of the lower extremities of the rabbit; secondly, to show the manner in which shrinkage of the insensitive area left after denervation takes place, and the parts played in this shrinkage by (*a*) recovery in the zone of overlap between the interrupted nerve and the neighbouring nerves; (*b*) recovery in the autonomous zone of the interrupted nerve; and thirdly, to show how recovery is affected by such factors as the nature of the lesion, its distance from the skin, age of the animal, and infection.

Methods

The rabbits used fall into two series: (1) 60 in which the nerves were cut but reunion was prevented by resection of several centimetres; (2) 94 in which the nerves were interrupted, either (*a*) by complete crushing at a single point with watchmakers' forceps (69 cases), or (*b*) by severing with scissors and suturing with concentrated plasma (22 cases) (Young and Medawar, 1940), or (*c*) crushing the nerve over a length of 4 cm. (3 cases). Series 1 was further subdivided into those animals in which the nerve whose sensory distribution was being studied was resected in order to delimit its autonomous zone, and other animals in which the nerve under study was left intact but all the nerves supplying adjacent skin areas were resected in order to delimit the maximal zone of the nerve in question.

All operations were performed aseptically under nembutal and ether anesthesia. At various times after operation the area of cutaneous analgesia was tested by pin prick. The needle was inserted vertically through the thickness of the skin, always working from the zone of sensory loss towards the sensitive zone. The points at which the first withdrawal reactions occurred were marked with indian ink or 30 per cent. silver nitrate. These single points were then joined by lines, which thus roughly mark the area of analgesia. Photographs were made as often as possible, or alternatively the areas were recorded on outline drawings of the rabbit's foot. For this latter purpose it was convenient to take measurements from certain points of the foot, namely, the external and internal malleolus or the line between them, the malleolar line, the base of the 5th metacarpus, the line of the tendon of the M. tibialis anterior where it crosses the malleolar line, and the crista tibiæ.

Before giving a detailed description of the results obtained in the individual nerves some general points may be mentioned which have to be considered in sensory tests on rabbits. The reaction of a rabbit to cutaneous nociceptive stimuli consists in an increase of the respiration rate, increased movement of the nares, and in local or general

withdrawal reaction. The intensity of reaction is not determined solely by the intensity of the stimulus. Age, race, and general condition of the animal have a definite influence on the kind and intensity of reaction. Younger animals generally react more briskly than adults, but the responses are sometimes more inconstant. Of the different races albinos are found relatively less reliable " witnesses " to pin stimuli. Yet even within a single race hyperreactive and hyporeactive types may be distinguished. General bad condition, caused by infection, sores, etc., undoubtedly raise the threshold of sensitivity. These variations have to be remembered when interpreting results such as are shown in the figures on the following pages. They also make it undesirable to repeat examinations at too frequent intervals: in nearly all our cases the tests have been done once a week. A further important point is that the various parts of the body have not the same threshold to nociceptive stimuli. In the posterior limb the sole and the areas below the outer and inner ankles are normally more sensitive than the dorsum of the foot or the anterior and medial parts of the leg. In the forelimbs the palmar aspect of the paw showed a lower threshold to pin-prick than the dorsum.

Peroneal Nerve

After isolated division of the peroneal nerve in the thigh the area of cutaneous analgesia at first extends over a large portion of the anterior surface of the shank as well as over the dorsum of the foot (Fig. 1). During the immediately succeeding days

FIG. 1.—Outline of the area of sensory loss after isolated section of the peroneal nerve, (*a*) lateral view, (*b*) anterior view. The shaded area is analgesic.

the area shrinks considerably, especially on the shank. The time and rate of this shrinkage shows clearly that it cannot be due to return of peroneal fibres to the area. The recovery of pain sensibility is therefore due to fibres passing in other nerves, particularly the lateral cutaneous nerve of the thigh which supplies the upper third of the shank. Indeed, the sensory loss in this area of the shank is very variable and depends to a certain extent on the amount of operative damage to other nerves. Thus, after high lesions of the peroneal, which involve an extensive opening in the thigh, the area of analgesia is always larger than after lesions at the level of the knee. In the first case the direct or indirect damage to the lateral cutaneous nerve of the thigh is presumably more extensive than in the second. When the operation is done quickly and carefully there may be a shorter period at which response to pin prick is entirely absent on the front of the shank. On the other hand, after manipulation of the neighbouring nerves the loss is especially profound and recovery is delayed.

It is not clear why " recovery " in such an intermediate area should not take place immediately after operation, except of course in cases of damage to the neighbouring nerves. It might be expected that the threshold of pain fibres running from the part of the skin of the front of the leg which is supplied by adjacent nerves would be unaffected by severance of the axons of the peroneal nerve, even though the two sets mingle in the cutaneous plexus. There is, however, some such disturbance, since the area of analgesia is greater in the days immediately after operation than later. In fact, the " recovery " of the pain fibres of the adjacent nerves proceeds progressively, occurring first in the upper part of the front of the leg, and last just above the malleolar line, i.e. in the area closest to the autonomous zone of the peroneal, where there are presumably the fewest intact fibres. It may be noted, however, that in a number of cases the whole intermediate zone, even after complete recovery, remained hypoalgesic. There is not sufficient information available to decide the nature of this " recovery " or adjustment of function of the undamaged overlapping fibres in an intermediate zone. We do not know to what degree it occurs centrally or peripherally but it will be seen later that the peripheral factor is very important.

Early shrinkage of the analgesia on the foot is less marked than on the front of the leg, and the area of overlap of the peroneal nerve with the sural on the lateral and the saphenous major on the medial borders is far less extensive than with the lateral cutaneous nerve of the thigh. Some 14 to 30 days after the lesion, in young animals even within a few days, when recovery in the intermediate zone is complete, there remains only analgesia of the autonomous zone of the peroneal. This extends over most of the dorsum of the foot, from the line between the malleoli downwards, but excludes small triangular areas in the inner and outer ankle regions which are supplied by the saphenous and sural nerves.

The participation of the peroneal nerve in the cutaneous supply of the rabbit's leg may also be shown by determining the maximal zone supplied by this nerve. After section of all adjacent nerves, i.e. tibial, sural, cutaneous femoris lateralis and saphenous major, the area of remaining sensibility has been found to include not only the whole dorsum of the foot but also the anterior, antero-lateral and antero-medial aspects of the leg, up to a level 38 mm. above the malleolar line. The response to pin-prick in the whole of this area is as brisk as in the corresponding areas of the normal leg. One day after operation some responses, though inconstant, have

been found as high as 58 mm. above the malleolar line.

Returning to the phenomena which follow a crushing of the peroneal nerve. After the early rapid recovery of pain sensibility on the front of the leg, there follows a period during which the margin of algesia remain about at the malleolar line. When a large section has been removed from the nerve the margin remains at this level indefinitely. There is very little penetration of fibres at this point from neighbouring nerves into the autonomous zone of the peroneal by local extension (Weddell *et al.*, 1941). However, if the peroneal nerve has been simply crushed, or the ends sutured after cutting, this period of waiting ends after a time which varies with the position and nature of the lesion. Indeed, it is not easy to determine the exact end. Once responses have begun to appear to pin prick in the autonomous zone there follows a more or less regular advance down the foot until the whole becomes sensitive. The advance is faster and more regular after a crush than it is after severance and suture. Figs. 2 (*a*) and (*b*) give good examples

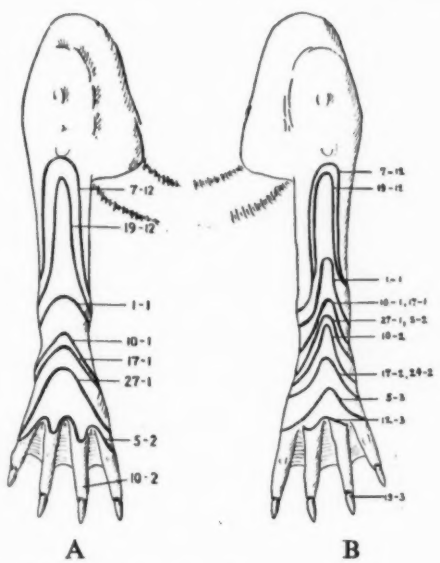


FIG. 2.—Diagrams showing the progress of recovery on the two sides of one animal (*a*) after crushing, (*b*) after suturing the peroneal nerve in middle of thigh. The operations were performed on 5.12.41, and complete recovery was recorded on 10.2.41 after the crush and on 19.3.41 after the suture. The pointers indicate the dates at which the various examinations were made.

of the two conditions. It is seen that recovery is slower after suturing even in the intermediate zone. This may be explained by the more extensive and longer manipulations which are necessary for suturing a nerve. After the crush each weekly examination showed some advance of the margin, whereas after suture there appeared to be periods of stagnation.

It has, however, been noticed that in all cases recovery proceeds from above downwards along the foot. The recovery is usually a little further advanced at the edges of the foot than at the centre of the area, which has the effect of producing the V-shaped lines shown. It is therefore not necessary to postulate that recovery takes place in any more complex manner than by simple growth of new fibres from the old trunks down into the plexuses.

In the distal parts of the autonomous zone of the peroneal nerve recovery of sensation proceeds somewhat quicker on the dorsum of the toes than in the digital interspatia, thus forming a wave-shaped line (Fig. 3).

During the study of recovery after lesions of the

FIG. 3.—Sensory recovery in the autonomous zone of the peroneal nerve after crushing in the middle of the thigh. The V-shaped line on the middle of the dorsum of the foot represents the border line of the analgesic area 53 days after operation, the wavy line represents the border line of analgesia 7 days later.

peroneal nerve the question arises, whether or not there is a period between arrival of fibres and their functional recovery. This question of a " peripheral delay " could be approached by calculations of rate of regeneration and by histological examinations. From the figures of Gutmann *et al.* (1942) we may calculate that after crushing the nerve at the malleolar line the first new fibres must have arrived back in the skin 7 days after the operation. Actually recovery in the autonomous zone start

as late as 12 days after operation (see Fig. 4). The extra period until recovery begins must be occupied either by slower growth of fibres within the skin, or in waiting for the arrival of a sufficient number of fibres. Since the pain fibres are presumably unmedullated there can hardly be any long period of waiting for maturation within the nerve trunk. Some indication of the time and nature of the "peripheral delay" may be found by histological examination. If a crush is performed high up in the thigh fibres should arrive in the main trunk on the dorsum of the foot about 60 days after operation (Gutmann *et al.* 1942). Histological observations showed that a piece of skin removed from the middorsum of the foot at this time does not contain

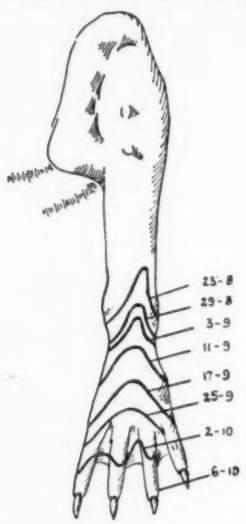


FIG. 4.—Diagram showing the progress of recovery after crushing the peroneal nerve in the malleolar line. The operation was performed on the 21.8.41, complete recovery was recorded on the 6.10.41. The pointers indicate the dates at which the various examinations were made.

any fibres. But in an animal in which a piece of skin has been removed 69 days after operation a few thin fibres may be seen, though most of the Schwann tubes contain no fibres. At this time the animal gives no response to pin prick. In a piece of skin from the same region removed 95 days after operation there are more fibres in the skin and they appear thicker, but many Schwann tubes still contain no fibres. No response to pin prick is obtainable at this time. The first positive response to pin prick has been obtained in one case 112 days after such an operation. The skin removed at this time shows a further increase in number of fibres. In this case it can thus be calculated that there is a period of about 40 days when, although fibres are present in the skin, no positive response is obtained. It is difficult to estimate the exact length of this delay as measurements of the length of the fibres in the skin can only be approximate and onset of recovery cannot be determined with exactness. However, it is clear that the delay is greater with the more distant lesions.

The histological findings indicate that the time between the arrival of the first fibres and their response to nociceptive stimuli is occupied by addition of new fibres and presumably a process of maturation. A certain number of fibres seems to be necessary before a positive response to nociceptive stimuli is obtainable. Thus one animal in which the peroneal nerve was sutured showed no recovery in the autonomous zone even 200 days after the operation although motor function had recovered at the usual time. Histological examination of a piece of skin removed from the middorsum of the foot showed that fibres were present in the skin but they were few and mostly thin.

Throughout this account we have not considered the possibility that some part of the sensory recovery in the denervated area is due to local extension of fibres into the denervated area from adjacent nerves (Weddell *et al.*, 1941). This factor may well play a part in the shrinkage of the autonomous area of the peroneal. The fact that in our cases, even in the absence of re-innervation through the peroneal nerve itself, the area of analgesia remains almost constant in the autonomous zone, shows that this factor operates only to a minor extent. However, in two animals in which no recovery due to regeneration was possible considerable shrinkage of the area of analgesia within the usual autonomous zone of the peroneal was found 6 months after operation, the line of analgesia running 9 and 12 mm. below the malleolar line. This recovery could be explained by extension of fibres derived from adjacent nerves.

Tibial Nerve

As this nerve is most frequently used in experiments on rabbits an accurate knowledge of its sensory function is of particular importance. Immediately after isolated section of the tibial nerve in the thigh an area of sensory loss is found situated over the medial two-thirds of the calcaneum, the medial half or two-thirds of the proximal and middle parts of the sole and the whole distal part of the sole except a narrow strip on the lateral border. There is also a small area of sensory loss on the medial border of the foot, encroaching on the inner ankle region and involving the proximal part of the 1st metatarsal. In the period following operation, however, a marked shrinkage of the area of sensory loss has been found in all cases, showing that there is an extensive overlap of the adjacent nerves, particularly the sural. A more or less rapid shrinkage of the zone of sensory loss is particularly obvious in the mixed zone between tibial and sural nerves, i.e. the lateral aspect of the heel and sole, forming a curved encroachment towards the medial aspect of the sole at the level of the 5th metatarsus (Fig. 5). On the other hand the border between the distribution of tibial and saphenous major remains constant for a longer time. Thus a bridge of sensory loss is formed between the sural and saphenous major distribution on the medial part of the proximal border of the sole and the foot. This bridge becomes gradually æsthetic, particularly in young animals, by the recovery of the zone of overlap with the sural nerve and by a time in which

no recovery by calculation due to regeneration could have taken place.

The extensive overlap, especially with the sural nerve, is also shown by determining the maximal zone of the tibial nerve. After cutting all nerves supplying adjacent skin areas (sural, peroneal, and saphenous major) a considerable extension of the maximal zone takes place in the days after the operation with the result that almost the whole sole becomes sensitive (see Fig. 6). The great practical importance of this extensive overlap between tibial and sural particularly in the heel region is obvious. Saving the sural nerve at operation in experiments on the tibial portion of the sciatic nerve either prevents completely or at least greatly delays and diminishes the development of a sore at the heel region, a development which only too often frustrates long lasting experiments in rabbits.

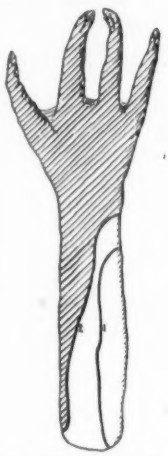


FIG. 5.—Outline of the areas of sensory loss on the plantar surface of the foot 1 and 17 days after isolated section of the tibial nerve. Line 1 represents the border of the analgesic area 1 day after operation, line 2, 17 days after operation. The shaded area represents the zone remaining analgesic 17 days after operation.

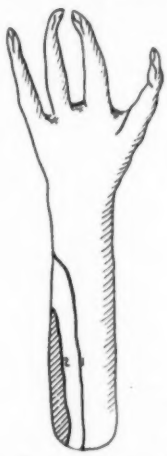


FIG. 6.—Outline of the areas of sensory loss 1 and 17 days after isolated section of the sural nerve. Line 1 represents the border of the analgesic area 1 day after operation, line 2, 17 days after operation. The shaded area represents the zone remaining analgesic 17 days after operation.

Sensory recovery in tibial lesions due to true regeneration may only be assumed when it proceeds in the distal third of the sole and along the medial side distally from a line corresponding with the 5th metatarsus. Recovery due to regeneration in the autonomous zone of the tibial advances in a centrifugal direction, as described in the process of recovery of the peroneal (Fig. 7). Again the margin of advance is not straight since recovery is a little more advanced at the sides than at the centre of the area.

Sural Nerve

The boot-shaped area of sensory loss following severance of this nerve and its rapid shrinkage have been described elsewhere (Weddell, Guttmann, and Gutmann, 1941). Shrinkage of the area of sensory loss after isolated section of the sural nerve is so extensive in young animals that the whole area of analgesia may recover within a period of a month. The details of the changes in the extent of the "autonomous" and maximal zone of the sural measured from the calcaneum to the distal boundaries of sensory change were measured in a 4 weeks old rabbit (No. 1). It is to be noted that the recovery of sensory function in the areas of overlap takes place not only in the distal part but progresses from the upper and also from the other parts of the denervated sural area. Data from a further animal (No. 2) illustrate the shrinkage of the "autonomous" zone only, measured from the calcaneum to both the distal and proximal boundaries of sensory change.*

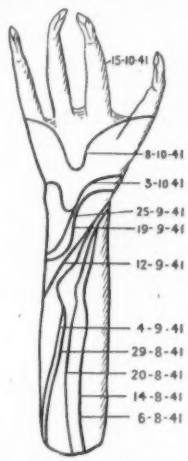


FIG. 7.—Diagram showing the progress of recovery after crushing the tibial in the lower third of the thigh. The operation was performed on 30.7.41, complete recovery recorded on 15.10.41. The pointers indicate the dates at which the different examinations were made.

RABBIT NO. 1.

Time of test after operation (days)	Extent of "autonomous" zone (mm.)	Extent of maximal zone (mm.)
1	21	30
8	16	34
15	15	39
19	7	41
26	0	41
31	0	41

RABBIT NO. 2.

Time of test after operation (days)	Extent of "autonomous" zone: distal boundary	Extent of "autonomous" zone: proximal boundary
1	30	33
5	30	33
15	20	17
18	18	15
20	14	13
25	10	10
28	0	0

The area in which sensation was restored, particularly the centre of the sural's cutaneous distribution below the outer ankle, was found hypo-

* The fact that sensibility returns rapidly throughout the analgesic area after severance of pure skin nerves particularly in young animals makes the term "autonomous zone" of doubtful significance (Weddell, *et al.*, 1941).

algesic compared with the analogous part of the opposite side. During the process of shrinkage after isolated section of the sural nerve the insensitive sural area above the outer ankle can be divided into two areas separated from each other by encroachments of overlapping nerves from either side.

The quick sensory recovery due to action of adjacent nerves makes it difficult to study the process of recovery due to regeneration of the interrupted nerve in young animals. An interesting feature during the course of recovery is a bridge formation

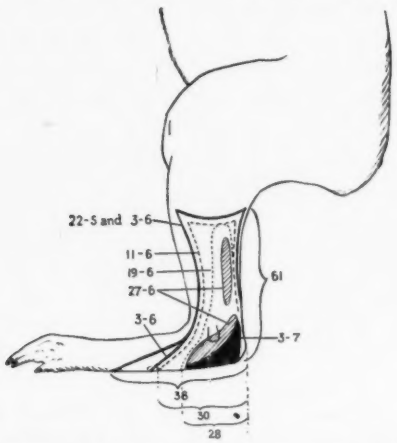


FIG. 8.—Diagram showing the progress of recovery after crushing the sural nerve in the lower third of the thigh. The operation was performed on 21.5.41, complete recovery recorded on 11.7.41. The brackets indicate the dimensions in mm. of the areas of sensory loss during the progress of recovery. The two cross-hatched areas and the black area are the areas of sensory loss found on 27.6.41, the black area alone represents the area of sensory loss found on 3.7.41. The pointers indicate the dates at which the different examinations were made.

in the lower third of the shank which separates two analgesic fields (Fig. 8), and is similar to that described after isolated section.

Postero-lateral Cutaneous Nerve of the Thigh

After isolated section of this nerve an area of analgesia was found occupying the greater part of the lateral aspect of the thigh and tapering to the upper third of the leg (Fig. 9, first line). The length

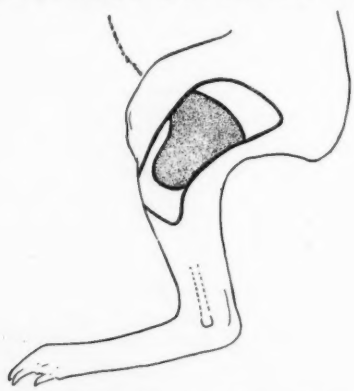


FIG. 9.—Outline of the areas of sensory loss 1 and 14 days after isolated section of the postero-latero-cutaneous nerve of the thigh. The shaded area is the area found analgesic 14 days after operation.

of the whole insensitive area found in this case 3 days after operation was 98 mm., its greatest width in the thigh was 37 mm. and on the leg 28 mm. In the period following operation a considerable shrinkage of both the proximal and distal borders of the area of sensory loss was found. Moreover the shrinkage is also obvious from the lateral border, particularly from the area of the antero-lateral cutaneous nerve of the thigh. Within a period of 14 days after operation the length of the insensitive zone has diminished to 59 mm. (Fig. 9, second line). The difference between the lines in the proximal part is 17 mm., that in the distal part 22 mm.

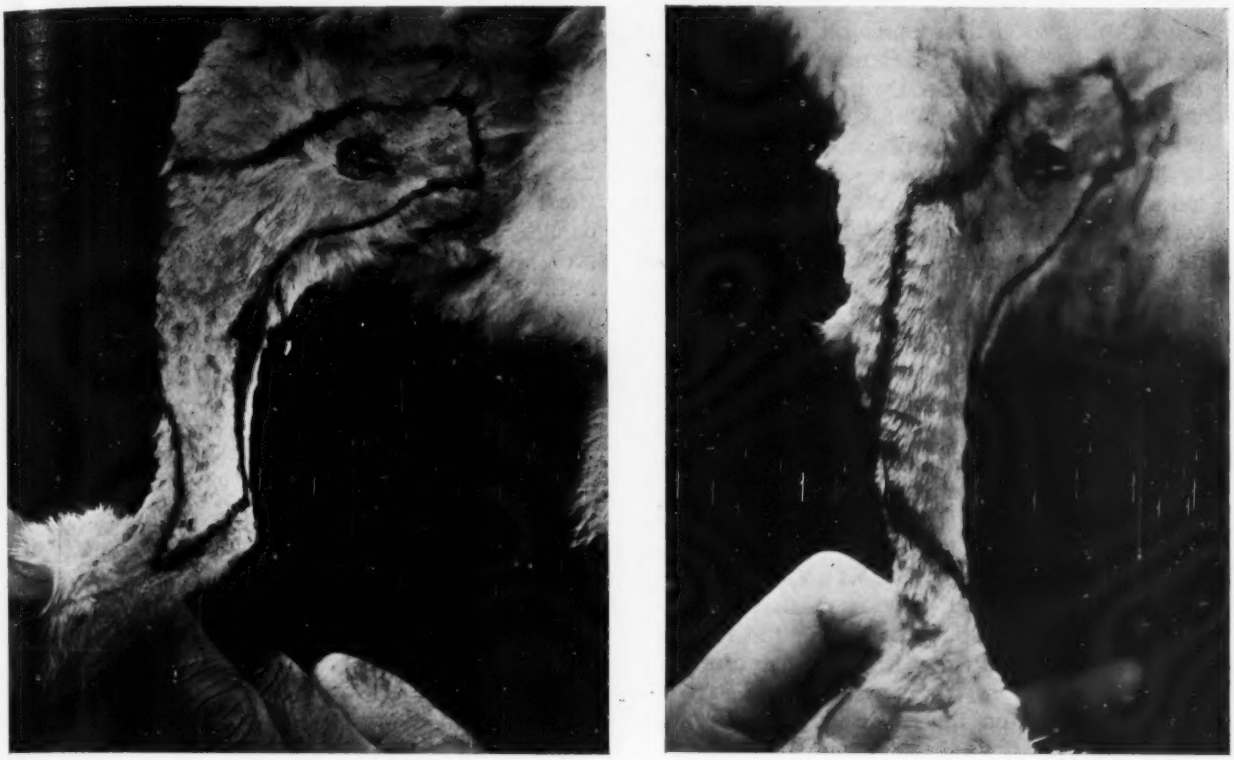
Saphenous Major

Fig. 10 shows the area of sensory loss after isolated

FIG. 10.—Outlines of the area of sensory loss 1 and 17 days after isolated section of the saphenous major nerve. Line 1 represents the border of the area of sensory loss 1 day after operation, line 2 the area of sensory loss 17 days after operation.

section of this nerve and the shrinkage at the proximal and distal borders 1 week after the operation. Fig. 11 (*a*) and (*b*) show that the anteromedial aspect of the shank receives fibres from both, the saphenous major and the peroneal nerves, a fact which is of interest in connection with the recovery in the area of overlap after peroneal lesion.

Fig. 12 demonstrates the sensory recovery after crushing the saphenous major in the groin. The zone of sensory loss found 1 day after operation



A B

FIG. 11.—Outline of the area of sensory loss immediately after isolated section of the saphenous major, demonstrating the participation of the nerve in the innervation of the anteromedial aspect of the shank: (*a*) medial view, (*b*) anteromedial view.

is very extensive. The shrinkage in the area of overlap begins very early after operation and the degree of shrinkage in the proximal as well as in the distal part of the area of sensory loss around the inner ankle is very remarkable in the first period after

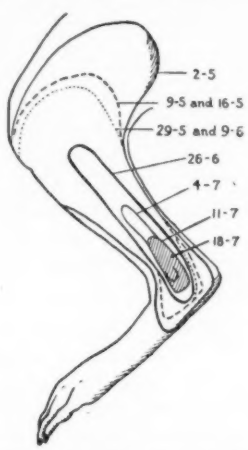


FIG. 12.—Diagram showing the progress of recovery after crushing the saphenous major in the groin. The operation was performed on 1.5.41, complete recovery recorded on 18.7.41. The shaded area is the area of sensory loss on 11.7.41. The pointers indicate the dates at which the various examinations were made.

operation. In the later stages of recovery, as described in other nerves, the shrinkage of the analgesic area progresses centrifugally and from either side. The case described shows a regular advance of sensory recovery. The centre of the autonomous zone of the saphenous major, localized around the inner ankle region recovers last.

The effect of various factors on speed and degree of recovery

1. *Type of lesion.*—A comparison between the course of recovery in a lesion in continuity on one side and division and suture of the peroneal on the other side is shown in Figs. 2 (*a*) and (*b*). In this experiment the peroneal nerve on the right side was crushed in the middle of the thigh with a fine watchmaker's forceps, and on the left side was cut at the same level and immediately sutured with plasma. Marked differences in time and degree (i.e. number and constancy of positive responses to pin prick, and the intensity of the reaction) of final recovery were found in favour of the lesion in continuity. Complete sensory recovery of the whole autonomous zone occurred after 67 days, whereas on the side of the severed and sutured nerve complete recovery took 104 days. The actual speed of advance of the line of analgesia within the autonomous zone on the sutured side was not much different from that on the crushed side, the main difference being that the advance began much later on the sutured side (see below p. 125). Even more obvious than the difference in time is the difference in degree of recovery. From the recovering autonomous zone of the crushed side the positive responses to nociceptive stimuli were

definitely more brisk and lively than on the sutured side. Moreover the responses on the sutured side were found to be more inconstant and sometimes deep pin prick elicited only a slow and sluggish withdrawal reaction. A further difference was found in the degree of trophic changes, particularly in the development of sores. Although peroneal lesions generally do not develop sores so easily as combined tibial and sural lesions they were found in some cases on certain places, i.e. dorsum of the toes and base of the 5th metatarsal. These trophic changes were found to be larger, and recovered more slowly, after division of the peroneal, than after crush.

In three animals sensory recovery was studied after crushing the nerve with large forceps over a length of 40 mm. on one side, and at a single point on the other. Onset of recovery in the autonomous zone was delayed on the side with the extensive crush for two weeks, and final recovery recorded 2 weeks later than on the side with the single crush. Even 200 days after the operation differences in the degree of recovery could be found, the responses being brisker on the side with the single crush.

2. *Recovery and age.*—Experiments to study the influence of age on the process of recovery were undertaken on rabbits about 1 month old. Recovery of sensation was followed after interruption of the peroneal, sural and tibial nerves. Eleven animals were operated on at different levels. In 3 animals with lesions of the peroneal nerve, after an initial shrinkage of the analgesic field below the malleolar line no further shrinkage could be observed although normal motor recovery occurred. No special reason for this stagnation in the process of recovery could be found.

The process of recovery shows the same general principles as described in adult animals. Shrinkage by recovery of the area of overlap in young animals proceeds very quickly. In 2 cases after peroneal lesions in the middle of the thigh the whole front of the shank has been found æsthetic even 3 days after operation. After crushing the peroneal nerve in the middle of the thigh recovery of the analgesic area was complete after about 1 month, compared with the average of 79 days in adult animals where the peroneal nerve has been crushed at this level.

After crushing the sural nerve in baby rabbits in the lower third of the thigh complete recovery was recorded in 1 month, compared with 43 and 51 days respectively after crushing the sural nerve in adults at this level. It may be noted, however, that such a speedy recovery of sensory function in the sural area has been, as mentioned before, observed in 5 cases in which the sural has been cut and resected and in which there has been no possibility of regeneration, except by local extension of fibres from adjacent nerves through the skin plexuses.

In contrast to the speedy recovery in baby rabbits the recovery of sensation in very old animals has been found to be delayed. These old animals are characterized by an ingrowth of nails and a sleepy behaviour. Case 570 was of particular interest. The sensory recovery was very delayed and in addition no motor recovery had occurred at the calculated time on the side on which a suture was made at the level of the knee. Diagnosis of failure of the junction was made. At reoperation, however, the junction was found very satisfactory and electrical stimulation above the junction showed definite contraction of the muscles of the peroneal group. Five weeks after this exploration recovery in the autonomous zone did actually begin, but was very delayed and complete only after 171 days. The degree of sensory recovery was particularly poor in the distal parts of the autonomous zone.

3. *Recovery and infection.*—No special experiments have been undertaken to investigate the effect of infection on the process of recovery but it has been possible to make some occasional observations on animals accidentally infected which allowed us to assess the influence of infection on the process of recovery.

The infections found were small abscesses confined to fascia or skin stitches, or superficial suppurations of the skin which later granulated. The abscesses frequently were encapsulated containing pus and Staphylococcus aureus. Abscesses confined to stitches or even big abscesses infiltrating the spaces between the fascia had no effect on the final recovery as long as there was no great pressure or interruption of the nerve fibres by the abscess. But there was usually a delay in the beginning of the first stage of recovery, namely in the area of overlap with adjacent nerves. Moreover in two cases besides the effect on overlap there were also abnormalities in the recovery of sensation due to regeneration. These cases will be described in detail.

In animal 469 the peroneal nerve was crushed on both sides at the same level. On the right side the following process of recovery was observed. Two months after operation there was still a big area of analgesia which included the dorsum of the foot and the anterior surface of the shank up to the crista tibiæ. Then a rather quick shrinkage set in and in 3 months after the operation only the dorsum of the foot distally to a line just below the malleolar line was analgesic. In the next month there was only slight shrinkage. The first positive response was obtained 12 mm. distal from the malleolar line and no further recovery took place. On the left side the same area of analgesia was found after the operation as on the right side. But after 54 days the first positive response was obtained in the malleolar line. A regular process of recovery in the autonomous zone followed, yet the recovery advanced exceptionally slowly. Total recovery was recorded after 132 days, a much longer time than was ever observed in other cases where the nerve was crushed at the same level. At biopsy a capsulated abscess 5×3 cm. in diameter, was found on the right side, partly infiltrating the peroneal nerve. Pinching the peroneal nerve in the shank did not elicit reflex responses. The first positive sensory reaction was obtained 60 mm. distal to the crush.

This case shows that on the infected side there was no recovery in the autonomous zone and even recovery in the zone of overlap was delayed. Moreover recovery was delayed on the uninfected side.

A different effect was observed in animal 546 in which the peroneal nerve was crushed on both sides at the same level. On both sides there was an analgesia of the foot and the anterior surface of the shank (Fig. 13, line 1). Recovery in the overlap zone set in very early and 5 days after the operation only the lower third of the shank was still analgesic (Fig. 13, line 2). Two weeks after the operation the animal became ill with a severe lymphangitis, edema of the shank and hydrocele. The skin was red and felt very hot, the animal was feverish and in bad condition. At the next examination 3 days later there was a complete analgesia of the dorsum of the foot and of the shank above the crista tibiæ on the uninfected side (Fig. 13, line 3). In the following days the edema diminished and the skin of the lateral part of the shank became necrotic. Very quick healing set in and new skin was formed which covered the defect. Recovery of sensation began again, proceeding in a regular way and being complete in 86 days on the formerly infected and 93 days on the uninfected side. Thus recovery in the autonomous zone proceeded even quicker on the infected side, being complete 1 week earlier than on the uninfected side.

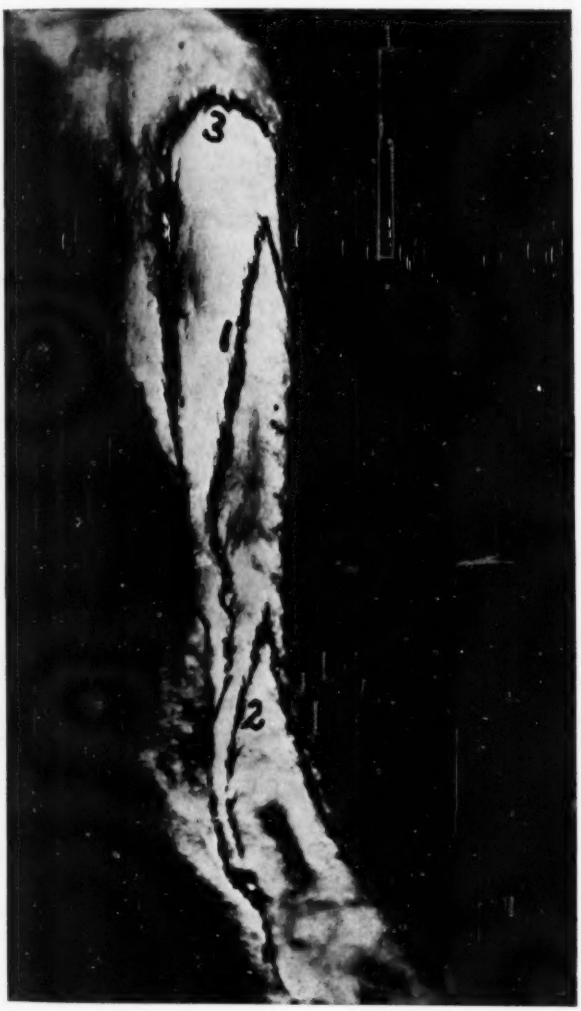


FIG. 13.—Shows the effect of infection on the recovery in overlap zones. Line 1 indicates the area of sensory loss 1 day after operation. Line 2, 5 days after operation. Line 3 the reversal of recovery after infection of the opposite leg.

Superficial infections (suppurating of the skin immediately after the operation) affect only the first stage of recovery, namely they delay recovery in overlap zones. This delay was found in 6 cases.

Rate of Advance of Sensory Recovery in the Skin

The rate of advance of "regeneration" in a nerve can be measured by a variety of methods, one of which is to record the advance of the margin of algesia over the skin (Gutmann *et al.*, 1942). The examinations made during the present investigation have given ample opportunity to expand the observations already reported and the results of these are given in Tables I and II.

TABLE I.—THE RATE OF RECOVERY IN THE AUTONOMOUS ZONE OF THE PERONEAL NERVE AFTER CRUSHING AT DIFFERENT LEVELS.

Animal	Length of autonomous zone	Recovery in days	Level of lesion	Rate mm./day	Average rate
582	60	34	Malleolar line	1·76	
674	64	23		2·78	2·26
677	74	33		2·24	
562L.	66	30		2·20	
560L.	55	22	At knee	2·50	2·20
494R.	59	31		1·90	
715L.	56	30		1·83	
714L.	70	30		2·33	
485R.	60	41	Middle of thigh	1·48	
579L.	69	36		1·92	1·86
690R.	48	28		1·71	
709L.	78	37		2·10	
689R.	58	36		1·67	
703L.	66	42		1·57	
704L.	73	45	High up in thigh	1·62	1·82
702R.	76	42		1·80	
509R.	80	35		2·29	

TABLE II.—THE RATE OF RECOVERY IN THE AUTONOMOUS ZONE OF THE PERONEAL AFTER SUTURING IN THE MIDDLE AND UPPER THIRD OF THE THIGH.

Animal	Length of autonomous zone	Recovery in days	Rate mm./day
485L.	30	60	2·00
486L.	37	55	1·49
569	56	78	1·39
589	47	66	1·40
604	34	68	2·00
670	56	62	1·11
		Average rate	1·57

Since the margin of recovery does not always advance smoothly it is clear that there are considerable difficulties in estimating the rate of regeneration by this method, these difficulties being of course

more severe after suture when the recovery is more irregular, than after a crush injury. Nevertheless by taking the same precautions in estimating each case much of the uncertainty may be eliminated. The rate of regeneration has been estimated by calculating the time taken for the margin of analgesia to advance from a definite datum line, i.e. the first line beyond which all recovery could clearly and unambiguously be ascribed to regeneration of fibres of the damaged nerve in the autonomous zone, to the tips of the toes. The examinations have been made weekly, and thus the time of " complete recovery " may have been over-estimated in cases in which recovery has been found nearly complete at one examination and complete at the next. This error has been avoided by taking in these cases the time of complete recovery as the mean of the last two observations. The distance between these lines, divided by the number of days involved, then gives an estimate of the rate of advance of the process of recovery of algesia as recorded in this way.

The rates given in Tables 1 and 2 have been calculated in this way. By measuring the distance between the lines recorded at intermediate examinations we can make estimates of the rate of regeneration over shorter periods. Fig. 14 shows a comparison of progress and rate of regeneration in the autonomous zone after crushing and after suturing the peroneal nerve. The figure shows graphically the later onset and slower progress of recovery in the autonomous zone after suturing the nerve. The late onset of recovery in the autonomous zone after suturing is of particular interest and indicates a longer waiting period ("peripheral delay") occupied, presumably by additon of fibres and a process of maturation. This period seems to be longer than after crushing. Calculating the time of arrival of the first axons in the beginning of the autonomous zone of the peroneal nerve below the malleolar line (Gutmann *et al.*, 1942) these should arrive there 41 days after crushing and 53 days after suturing the nerve. From Fig. 14 it can be seen that recovery in the autonomous zone actually starts in the 6th week after crushing but is declared till the 11th week after suture.

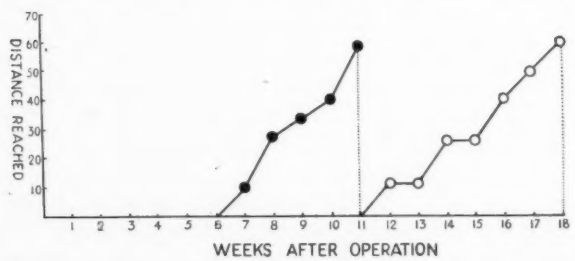


FIG. 14.—Diagram to show the onset and rate of recovery of sensation in the autonomous zone after crushing (line with black circles) and after suturing (line with white circles) of the peroneal nerve in the upper third of the thigh. The ordinates indicate the distance of the line of analgesia in mm. from start of the autonomous zone, the abscissæ the weeks after operation. The dotted lines show the time at which recovery was found to be complete. Note slightly steeper slope of the line, earlier start of recovery in autonomous zone and quicker complete recovery after crushing the nerve.

The estimates show more irregular fluctuations than those obtained by the consideration of longer distances and times, and no doubt part of this fluctuation is due to errors of testing and random change in the state of the animal. Especially after sutures there are periods during which the margin of algesia changes little or not at all, and others in which it moves forward fast, almost by jumps.

Not enough animals have been examined to decide the question whether recovery of sensory function proceeds at a different rate after lesions of different nerves, but no very obvious signs of differences have appeared. Thus in 4 animals in which the tibial nerve was crushed about 200 mm. from the end of the toes the average time of final recovery was 72 days compared with 78 days after peroneal lesions made at the corresponding level.

In attempting to summarize these figures we may consider (1) the average rate recorded from all cases in which the peroneal nerve was crushed, at whatever level: $1{\cdot}98 \pm 0{\cdot}09$ mm./day. (2) The average rate from all cases in which the peroneal nerve was severed and sutured: $1{\cdot}57 \pm 0{\cdot}15$ mm./day. In Table 1 the results are also classified according to the level of the lesion, and although the results from each level are rather few they show a tendency to lower rates from the more distant lesions. This is a most interesting result for the solution of the problem of the effect of distance on rate of regeneration.

As has already been pointed out (Gutmann *et al.*, 1942) the question of whether the rate varies with the level of the injury cannot be settled by dividing time for recovery into distance from lesion to endorgan. If this were done the delay in the scar and in the end organ would enter in varying proportional extents into the calculation. In the present instance, however, where the rate is estimated between two points on the skin all other factors except distance can be regarded as constant. The results therefore suggest that regeneration in skin becomes slower as the distance between lesion and endorgan increases. This might be due to various factors, for instance, the increasing length of the nerve to be " maintained," the greater collapse of the Schwann tubes into which new fibres must grow (Holmes and Young, 1942), or the greater scatter in time of arrival of fibres in the skin. We shall see that the first two factors mentioned probably do not operate.

A further question is whether the rate of advance of regeneration in the nerve becomes slower towards the periphery. This can be examined by plotting the time necessary for complete recovery of algesia against distance of the lesion. This was the method previously adopted (Gutmann *et al.*, 1942) to determine the rate of advance of functionally completed sensory fibres in the nerve. Further figures of the same sort are now available and given in Fig. 15. The most interesting feature in which these results add to those already published is that they include figures for the time of recovery after crushing the

peroneal nerve at the malleolar line. We therefore have a set of data of the time necessary for recovery after lesions at a wider range of distances from the end organ (69 to 282 mm.) than it is possible to obtain with any other technique in the rabbit. If the rate of regeneration is slower the longer the stretch of nerve which must recover we should expect that the points of Fig. 15 would not lie as a straight line. Unfortunately the data show too much scatter to enable this to be tested directly. However, inspection of the graph gives the impression that the rate of regeneration in the nerve does not fall off seriously as the distance to be repaired increases. If then we assume a linear relationship, the calculated rate of regeneration, including all animals in which the peroneal nerve has been crushed, is $2{\cdot}48 \pm 0{\cdot}26$ mm./day, which agrees

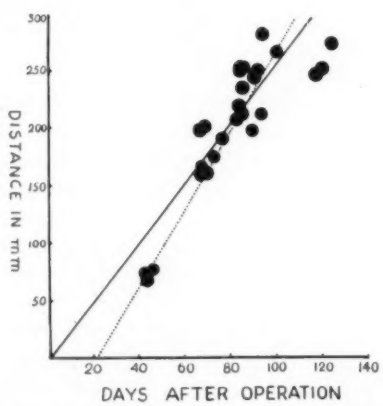


FIG. 15.—Graph showing the times of complete recovery plotted against level of the lesion after crushing the peroneal nerve at varying distances from the skin of the toes. The full line is the regression line, arithmetically calculated for all the points, the dotted line is fitted so as to pass through the low readings.

reasonably with that already given of $2{\cdot}74 \pm 0{\cdot}44$ mm./day. However, it will be noticed that arithmetic calculation of the regression line has failed to give due weight to the three observations in which the nerve has been crushed very low. If we drew a line to pass nearer these points (which cannot be greatly in error) the rate would appear higher and the latent period longer. The dotted line shown in Fig. 15 is drawn in this way and gives a rate of regeneration of 3·35 mm./day and a latent period of 22 days. These are probably better estimates than those arithmetically derived. This estimate agrees closely with the results from the paired data (Gutmann *et al.*, 1942) obtained by crushing the peroneal nerve high on one and low on the other side of the same animal, which gave a rate of regeneration of 3·39 mm./day.

Fig. 16 shows the results after severance and suturing of the peroneal nerve. The data include only one case in which the suture was done at the malleolar line and thus calculations of a regression line would be invalidated by an overweight of the cases in which sutures were performed higher up in the thigh. Further sutures were attempted at the malleolar line, but suturing a thin nerve at a point of mechanical stretch proved to be technically difficult and only the one satisfactory result has been achieved.

Including the datum from the suture at the malleolar line it appears to be difficult to fit a straight line, and the impression is gained that the rate falls off, being slower with the more distant lesions. As a compromise, therefore, the best possible line has been fitted to all points but so as to pass through the lowest point, which in any case cannot involve great error. This gives a rate of regeneration of 2·46 mm./day which is slower than after crushing and gives a definitely longer latent period, 40 days.*

Sensory recoveries after suture show serious variations which seem to be characteristic of this procedure. In view of these variations it did not seem likely that it would be possible to obtain more

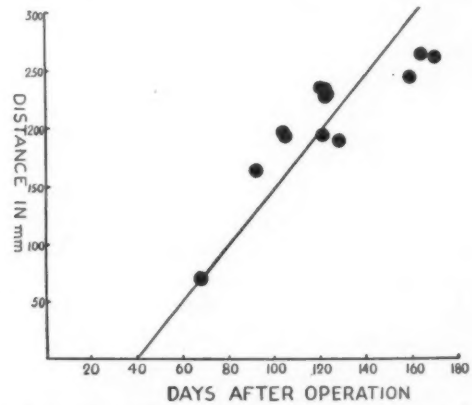


FIG. 16.—Graph showing the times of complete recovery plotted against level of the lesion after severance and suture the peroneal nerve at varying distances from the skin of the toes.

satisfactory data. Moreover, it must be remembered that calculation of the rate of regeneration made from these data rests on the assumption that it is constant over the whole stretch of the nerve. But, as pointed out, the data suggest a falling off of the line with the more distant lesions.

It can be concluded therefore that the rate of regeneration is slower after suturing than after crushing, that the latent period is longer after suturing, and that the rate of regeneration possibly falls off with the more distant lesions.

The data and those obtained from observations on recovery of motor function (Gutmann *et al.*, 1942) allow a comparison of the rate of functional regeneration of motor and sensory fibres. The paired data obtained from observations on recovery of motor function give a rate of 3·10 mm./day, those from observations on sensory recovery 3·39 mm./day. A similar difference appears between the rates calculated from all data available, namely, 2·77 mm./day for motor fibres (Gutmann, 1942) and 3·35 mm./day for pain fibres. A slightly quicker recovery of pain fibres, these being the only ones

* A single observation only was available of an animal in which the peroneal nerve was sutured high on one and low on the other side. The rate of regeneration calculated from this experiment (Gutmann *et al.*, 1942) was 2·0 mm./day.

we are considering in our sensory examinations, is to be expected as they are presumably unmedullated or thinly medullated fibres and their functional completion (Gutmann *et al.*, 1942) will therefore need less time than that of the thicker and medullated motor fibres.

Discussion

Recovery of analgesic areas after nerve lesions in the rabbit may be said to take place by two processes. (1) By recovery due to compensatory action of the neighbouring nerves. (2) By recovery due to regeneration of the interrupted nerve in the autonomous zone.

1. *Recovery due to action of neighbouring nerves.*

(*a*) *Recovery in overlap areas.*—These areas naturally tend to occur chiefly where several nerves meet thus forming intermediate zones. According to the anatomical distribution of the overlapping nerves characteristic patterns of the intermediate zones in the sensory supply of individual peripheral nerves are found. Pure cutaneous nerves such as the sural, internal saphenous and lateral cutaneous nerve of the thigh show extensive overlap on both the proximal and distal borders, whereas in mixed nerves such as the tibial and peroneal the overlap in their distal distribution is far less or almost negligible. Accordingly the exact pattern of recovery due to overlap depends on this anatomical arrangement.

Although the intermediate zones contain intact fibres for the whole time after operation they do not immediately become responsive. In young animals their recovery may be complete within a few days. Thus the whole of the front of the leg of 2 rabbits, 1 month old, showed responses 3 days after interruption of the peroneal nerve. More usually, however, the fibres within these zones only become fully responsive after 2 to 4 weeks, the rule being that those in the areas nearest to the autonomous zone recover last. The question arises what process of readjustment occurs during the "recovery" of an intermediate zone. It might be in the skin itself, in the nerve trunk or in the C.N.S. That the peripheral factor is a very important one is shown by the fact that recovery of overlap zones is slower when the neighbouring nerves have been damaged by handling at the operation. On the other hand any factor which raises thresholds throughout the body (narcosis, infection, age, or general bad conditions) may also cause a reversal of recovery in an intermediate zone, even though it does not directly damage either the skin or the nerves. These overlap zones, therefore, when one of the nerves to them has been cut, contain too few fibres to function properly. It was particularly striking after peroneal lesions how long the large intermediate zone of this nerve over the antero-lateral aspect of the shank, remained hypoalgesic after recovery.

(*b*) *Recovery by extension of fibres from adjacent nerves.*—A further factor in the "recovery" due to action of adjacent nerves is the process of extension of fibres into the autonomous zone. There is little to add on this subject to what has already been said (Weddell *et al.*, 1941). The process is naturally seen at its most marked where a small zone of loss of sensation is surrounded by other nerves, e.g. in the sural nerve. We have confirmed that the autonomous zone of this nerve may become completely sensitive even in the absence of any possibility of growth down the nerve trunk. This was found particularly in young animals. But certainly the local extension cannot replace regeneration through the nerve in the recovery of larger areas. In mixed nerves such as the peroneal the extension of fibres from adjacent nerves into a denervated area is at most of subordinate importance for restoration of sensory function. Thus in 4 animals recovery through the peroneal nerve could not take place, and the margin of analgesia remained approximately at the malleolar line for 180 days.

2. *Recovery by regeneration of the nerve.*

Recovery within an analgesic autonomous zone due to true regeneration advances approximately from above downwards in all the examined nerves of the rabbit. The forward advance is most marked in the areas at the extremities of the limbs. In all the areas and especially those which are broad and lie higher up the limb, the margin of recovery advances faster at the edges than the centre of the area, so that towards the end recovery proceeds more or less "concentrically." This phenomenon is observed in the recovery of many areas in man. The exact pattern of recovery will depend on the anatomical arrangement of the branches within the area. Thus observations on recovery of sensation show that the visible pattern of recovery, consisting in centrifugal advance and concentric shrinkage is the same after lesions of all nerves.

The margin of algesia makes a general advance, however, which is sufficiently clear to allow estimates of its rate. As already pointed out (Gutmann *et al.*, 1942), the rates which we have obtained are not very different from those which can be calculated from the results of other workers, e.g. Trotter and Davies (1909) on the human skin.

Careful use of the method of studying rate of advance of the algesic area on the dorsum of the foot of the rabbit gives a method for studying the effect of various factors on the process of sensory recovery. The nature of the lesion appears to be the most important of such factors. After crushing the nerve at a single point recovery advances on the foot quicker than after severance and suture. Moreover in the second case there are fewer points from which response can be elicited. These differences agree with those which have been found in all the studies on rate of regeneration (Gutmann *et al.*, 1942) and one of us (Gutmann, 1942) has recently found exactly comparable differences in studies of motor recovery. It is not possible at present to be certain of the reason for the great success of nervous regeneration after a nerve has

been crushed at a single point. The Schwann tubes maintain their continuity after such an operation (Young, personal communication), and it seems probable that the good regeneration is due largely to the large number of correct re-connections which it allows.

This is substantiated by analogous clinical observations made by one of us (L.G.), in cases of complete lesions in continuity of the musculospiral nerve due to alcohol or CO_2 intoxication and others following fracture of the humerus in the middle of the upper arm, also recently in a case of a plexus lesion of inflammatory genesis (Guttmann and Pennybacker, 1942). All these cases showed the classical signs of a complete lesion but made an excellent and complete functional recovery. On the other hand there are lesions in continuity after crushing which only show imperfect functional recovery similar to that found after division of the nerve. These are cases in which considerable length of nerve has been crushed, probably producing rupture of a greater number of Schwann tubes and therefore giving less chance of correct re-connections. In this connection the cases described here of delayed and imperfect recovery in rabbits after extensive crushes are of interest.

The distance of the lesion from the skin plays a part in determining the speed of advance of recovery, the more distant lesions showing a slower advance of margin of recovery in the skin and perhaps also in the nerve trunk. This is probably to be interpreted as due to the scattered arrival of new fibres, though this cannot be decided for certain.

Summary

1. The maximal and autonomous zones of the cutaneous distribution of various peripheral nerves of the rabbit have been determined and the process of recovery of cutaneous sensation to nociceptive stimuli studied after interruption of these nerves.

2. Recovery of sensation in an analgesic area is a complex process comprising three main phases: (1) Recovery in zones of overlap by the progressive resumption of function by fibres of adjacent nerves. (2) Extension of these fibres into the denervated area. (3) Regeneration of the interrupted nerve.

3. Recovery in zones of overlap occurs generally 2 to 4 weeks after interruption of the nerve although in young animals it may occur within a few days after operation.

4. Recovery in zones of overlap is peculiarly susceptible to various factors such as local damage of the skin supplied by adjacent nerves, transient block of these nerves as a result of operation and all processes which tend to raise nervous thresholds such as infection, sores, narcosis, and age.

5. Recovery in the autonomous zone of a nerve due to regeneration of the interrupted nerve proceeds in general in a downward direction. Especially in large areas recovery often advances faster at the edges than in the centre, so that the analgesic area shrinks concentrically. The visible pattern of recovery, consisting in centrifugal advance and concentric shrinkage is the same after lesions of all nerves.

6. The nature of the lesion is of decisive importance for time and degree of recovery. After suturing recovery is slower, more irregular, and the degree of recovery is definitely less than after crushing.

7. Crushing the nerve over a stretch of 4 cm. delays recovery by 2 weeks and is followed by a lower degree of functional recovery compared with recovery after a single crush.

8. Study of the time of recovery after lesions at different levels gives an estimate of the rate of progress of functional regeneration down the nerve of 3·35 mm./day with a latent period of 22 days after crushing and 2·46 mm./day with a latent period of 40 days after suturing. Great variabilities after suturing make this estimate less reliable than after crushing.

9. The average rate of advance of the margin of algesia in the autonomous zone on the dorsum of the foot in 17 animals after interruption of the peroneal nerve at various levels is $1{\cdot}98 \pm 0{\cdot}09$ mm./day when the nerve has been crushed and $1{\cdot}57 \pm 0{\cdot}15$ mm./day in 6 cases when it has been cut and sutured.

10. The rate of advance of the margin of algesia is higher (2·3 mm./day) when the nerve is crushed at the ankle than when it is crushed in the thigh (1·8 mm./day).

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THE CHEMICAL INHIBITION OF FIBRE REGENERATION AND NEUROMA FORMATION IN PERIPHERAL NERVES

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Introduction

THE problem of suppressing the regenerative growth of nerve fibres by chemical or other means owes its clinical interest to the need for preventing or stopping the acute pain that sometimes develops after injury to peripheral nerves. The conditions under which acute pain develops have not been closely defined. It cannot be definitely attributed to any *one* particular cause, and it is not invariably accompanied be neuroma formation. Reactions from islands of infection and foreign bodies in the nerve itself (Marinesco 1918, 1920), the involvement of escaping nerve fibres in scar tissue and muscle (discussed by Corner, 1918b), and pressure upon "young" unmyelinated fibres (Cone, 1918) may each play a part. Clinical evidence nevertheless shows that pain in some form, particularly in amputation stumps, is associated with neuroma formation and other consequences of unorganized regenerative growth. Pain of this sort is sometimes relieved by excising the neuroma, and is prevented from recurring, or from arising in the first instance, by taking certain preventative measures. These may be reviewed shortly under two headings:

A. Surgical and Mechanical

Diversion of the free end of the nerve, with or without resection, into a position where it is protected by muscle bellies and free from violent pressure and movement; or into bone (Seddon, 1941), where it may come to no harm. Implantation of the central stump into muscle (Moscowicz, 1918). Crushing (Kruger, 1916) or ligating the central stump. Closure of the open end of the central stump by ligating an epineurial sleeve slipped over the end of the nerve (Chapple, 1918), or by suturing the "trapdoor" flaps left after excising a wedge-shaped piece from the tip (Corner, 1918a). Reflection of the nerve into or through itself (Bardenhäuer, 1908 *).

The more radical of these methods have been severely criticized by Huber and Lewis (1920), Stookey (1922), and others. At the other extreme, leaving the nerve as far as possible alone may be regarded as a calculated surgical procedure.

B. Physical and Chemical

Coagulation by cauterization or the intraneural injection of hot water has been described by Hedri (1921), Erlacher (1924), and Lexer (1931). Laewen (1925, 1930) claims that freezing the sciatic nerve in man for 4 to 6 minutes abolishes conduction for 1½ to 2 years, though interruption by cold is more generally regarded as being only temporary in effect.

The chemical reagents injected into nerves for the relief of pain and for preventing neuroma formation belong, with few exceptions, to the class of *coagulants*. Ethyl alcohol has been used for the treatment of causalgias (Sicard, 1916), neuralgias (Schlosser, 1903; Harris, 1909; Patrick, 1912; May, 1912), and for the injection of amputation stumps (Sicard, 1916; Huber and Lewis, 1920; Huber, 1927; Foerster, 1929; Beswerschenko, 1929). Experimental and histological studies of its action on nerve have been made by Finkelnburg (1903, 1907), May (1912), Bersou (1912); the most detailed and complete analysis is that of Huber and Lewis (1920), reported with full protocols by Huber (1927). Other fixatives and coagulants whose effects on nerve regeneration have been studied experimentally or clinically include: Osmium tetroxide (osmic acid), Neuber, 1883; Fraenkel, 1884. Mercuric chloride (mercury perchloride), Erlacher, 1924. Phenol (carbolic acid), Benedict, 1922; Frankenthal, 1928; Beswerschenko, 1929. Formaldehyde, Erlacher, 1924; Foerster, 1929; Beswerschenko, 1929.

The procedures reviewed under headings A and B have different objects. Resection of the stump or insertion into bone may be thought of as methods for putting the nerve out of harm's way. Ligation, the surgical closure of the end of the stump, and Bardenhäuer's operation are designed to prevent the escape of fibres, since they will certainly not prevent neuroma formation. The chemical methods are the most radical, since their object is to abolish living fibres from the terminal stretch of the nerve.

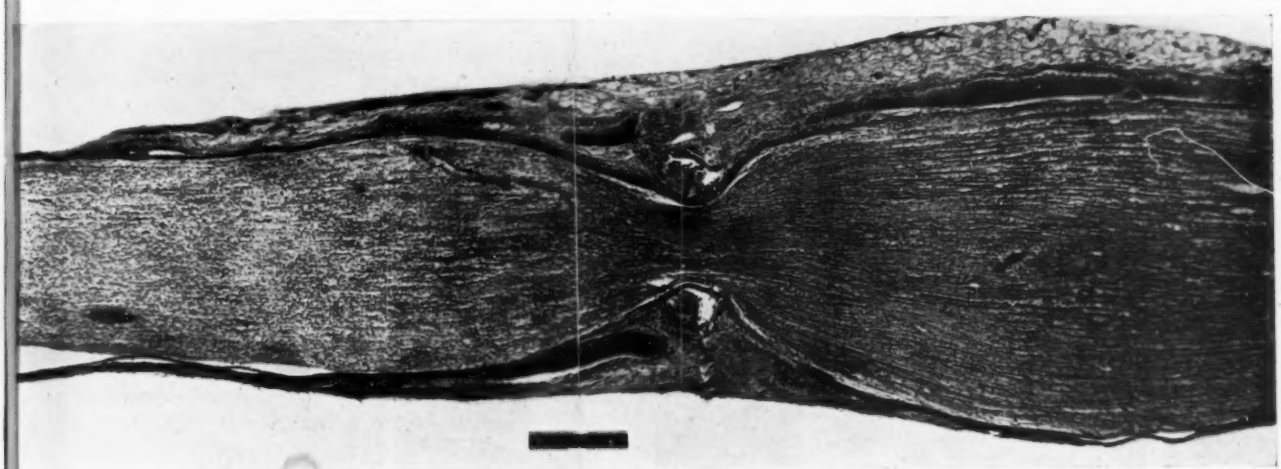
The experiments described in this paper, which follow in main outline those of Huber and Lewis (Huber, 1927), are chiefly concerned with the injection of chemical substances into the tibial division of the sciatic nerve of the rabbit. Their main object is to find out which reagents among a range of reasonable choice inhibit the regenerative growth of axons for the longest time. There is no ground for believing that *permanent* inhibition can be brought about by any method not involving the destruction of the cell-body of the neurone. Isolated clinical examples (e.g. Dustin, 1918) and animal experiments (Holmes and Young, 1942) show that the central stump of a divided nerve retains its power to reinnervate the periphery for a long time after

* We have tried to examine the rationale of Bardenhäuer's and similar operations by a series of experiments in which the central stumps of the tibial and peroneal divisions of the sciatic nerve of the rabbit were sutured into each other through an intermediate stretch of autograft. Multiple bulb formation with gross fibre abnormalities accompanied by whorling and deviation of the fibre bundles were the rule. We found no evidence that regenerating fibres could enter a common endoneurial pathway from opposite ends and block each other in the middle, although from what is known of fibre regeneration rates in rabbits (Young and Medawar, 1940; Sanders and Young, 1942; Gutmann, Guttmann, Medawar, and Young, 1942) they should in theory have had an opportunity to do so.

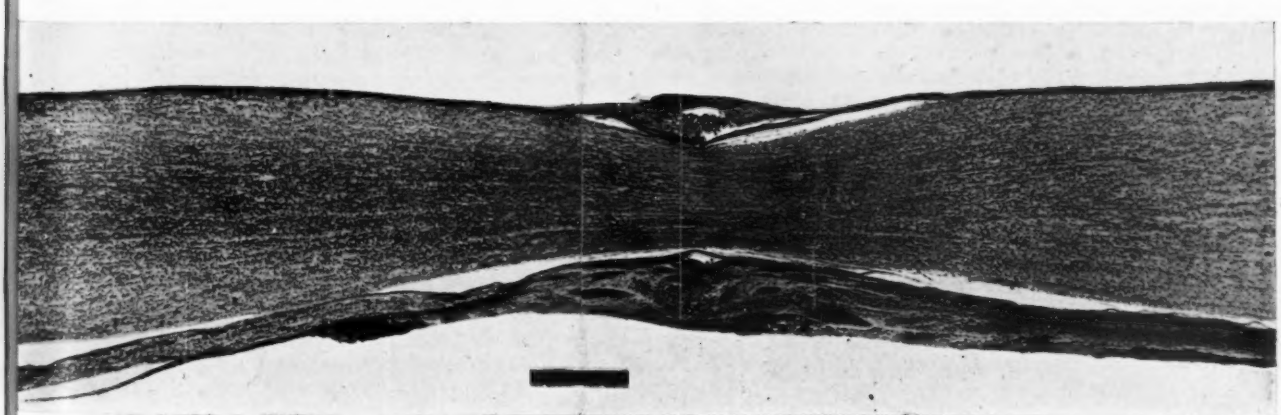
division; and while this power may very well decline over the whole life span, as the power of repair in general is known to do, the decline can hardly be significant from a clinical point of view. A second object of these experiments has been to examine the relationship between axon regeneration, neuroma formation, and the tendency of nerve to become heavily involved in and adherent to the tissues in its neighbourhood; and in laboratory animals, it is possible to make a clearer distinction between the effects of nerve damage and those of collateral injury than is possible by clinical observation. On the other hand, the problem of the origin of pain cannot be solved by animal experiments alone.

The Etiology of Neuroma Formation

A well-marked swelling almost invariably forms at the end of the central stump of a divided nerve, though it may later subside. Under favourable circumstances, the development of this swelling may be only incidental to the process of repair after an operation of grafting or suture, but the regenerative growth of fibres takes place irrespective of whether they regain their normal path of growth or not. The formation of a central end bulb is the response of growing fibres to interference in their path of growth. Careful *pinching* of a nerve may interrupt all the fibres while creating no serious obstacle to their subsequent regeneration. Under these circumstances, no central swelling is formed. On the other hand, the constriction of a nerve with a very tight ligature (Fig. 1, A) invariably leads to the formation of a local swelling immediately central to the point of ligation. If two such ligatures are tied 10 to 20 mm. apart in such a way that no fibres can escape through the upper one, or if the nerve is interrupted without section by applying a drop of chromic acid well above a single ligature, then no swelling develops at the lower interruption (Fig. 1, b). The experiments on chemical inhibition described below confirm and reinforce the fact that in the absence of fibres, a central end bulb is not formed, although there is no reason why we should not expect a swelling to form



A



B

FIG. 1.—(A) 25 days after tying a tight ligature round the tibial nerve of the rabbit: central and peripheral swellings about the plane of the ligature. Regenerating fibres have just begun to force their way through the hour-glass constriction.

(B) 25 days after tying a similar ligature round a stretch of nerve which has been "sterilized" by tying a tight ligature central to the one illustrated here. No swellings form.

The central stump lies to the right. Scale 0·5 mm. Bodian's stain.

by the proliferation of endoneurial and other connective tissue elements, and in particular of Schwann cells. The problems of inhibiting neuroma formation and of suppressing the regenerative growth of axons, which Stookey distinguishes, are therefore coextensive in scope.

Experiments on Chemical Inhibition

Technique: The sciatic nerve of the rabbit is exposed by an incision parallel to and just inside the margin of the femur, and the tibial division separated from the peroneal down the length so exposed. The tibial is raised and packed with moist gauze around all surfaces except the upper. In this position the nerve can be safely injected with 0·1 to 0·2 ml. of fluid, and either subepineurally or intraneurally. In the former case, the injection fluid travels 60 mm. or more along the highly permeable epineurial lymph spaces and destroys a corresponding length of nerve. In the latter, the injection fluid forms a localized bulb, which does not usually collapse when the needle is withdrawn, and which forms a local reservoir of high concentration. After a single injection by one or the other of these methods, the nerve is cut at, or not more than 10 mm. below the injection point, and replaced parallel to but not in contact with the peroneal. In a few cases (cf. Huber, 1927) the nerve has been left uncut after injection in order to give the central stump the most favourable chance, under the circumstances, of reinnervating the periphery.

In the majority of experiments, the animals were re-examined after two months, a period more or less arbitrarily chosen in the first place as the earliest at which an indicative result could be expected. If a neuroma had formed after two months, it was excised and examined histologically. If not, the animals were allowed to survive for periods up to and in many cases exceeding a year.

Controls: The behaviour of the sciatic nerve of the rabbit after simple section and resection has been studied by Huber and Lewis (1920) and reported in detail by Huber (1927). An extensive series of neuromas formed within 50 days of section are available from other experiments done in this department; and in addition to these, twelve long-period controls have been laid down. They differ from those of Huber and Lewis in being concerned only with the tibial division of the sciatic nerve, in extending over a wider range of time (103 to 457 days), and in the relatively large gaps (30 to 40 mm.) left between the stumps after resection. These controls, taken in conjunction with the experiments using reagents which proved to be ineffective, make it possible to draw a clear-cut distinction between " successful " and unsuccessful inhibitions (see below, p. 134).

Histological techniques : After fixation by the formol-alcohol-acetic mixture recommended by Bodian (1936) or by formol saline, serial longitudinal sections of the histological material have been stained by the methods of Bodian or Holmes (1942) respectively for the demonstration of axons. Where sufficient material has been available, alternate slides have been stained or counterstained by hæmatoxylin and eosin or Masson's trichrome stain.

The choice of reagents.—An inhibitor for injection into nerves should be one which is capable of forming a persistent compound or adsorbate at the site of injection, and which is highly toxic at low concentrations. Fixatives and certain powerfully adsorbed dyestuffs satisfy these conditions, and the majority of the substances whose use is described below come under the former category. Apart from fixatives, the effects of certain other reagents have been examined ; and though their selection may be regarded as arbitrary, some sort of theoretical justification for their use could be brought forward in each case. Sodium taurocholate, for instance, is powerfully surface-active, and should therefore inhibit very strongly the amœboid movement which takes place at the tip of the growing axon (Speidel 1932, 1933). Again, aldehydes as a class are powerful inhibitors of growth and cell movement (Boyland and Mawson, 1938 ; Pomerat and Willmer, 1939; Medawar, 1940). Substances other than fixatives have however proved unsuccessful in practice, and in some cases have led to highly undesirable secondary reactions which are uniformly lacking when fixatives are used. This may be because fixatives are themselves " fixed " by the tissues they act on, so that their destructive effects are sharply local.

Fixatives are themselves a very miscellaneous collection of compounds, but in some cases it has proved possible to correlate their physico-chemical properties with their action *in vivo.*

Summary of Results

Long-period controls.—Huber and Lewis noted the formation of end bulbs or spindle-shaped enlargements in all but one of their set of 20 controls, the exception being the longest-period animal (1 year) in which complete reunion between the stumps had taken place. Large end bulbs (some of which are illustrated in Fig. 2, **1** to **6**) have been found in all but one of the 12 long-period controls laid down by us, and in 6, equally distributed throughout the age series, a resection gap of 30 to 40 mm. (15 to 25 times the diameter of the intact nerve) had been bridged by new growth and fibres had entered the peripheral stump (Fig. 2, **1**, **4**, **6**). As a general rule, the largest bulbs, 4 to 6 mm. in maximum width, were found on central stumps with no morphological connections to the peripheral stumps; and these showed the heaviest adhesions to muscle and fascia. The detailed anatomy of neuromas of section has been investigated by Dustin (1918), Cone (1918), Huber and Lewis (1920), and many others. Tracing the fibres from the centre towards the periphery we may usually distinguish (*a*) a normal zone of parallel fibre orientation ; (*b*) a " flare " zone, corresponding to the central end of the bulb, where the fibre tracts fan out symmetrically and there is marked proliferation of endoneurial connective tissue ; (*c*) a plexiform zone, where small bundles of fibres undergo chaotic deviations and criss-crossing, often turning back on themselves ; and finally (*d*) a zone of involvement, where a comparatively small number of fibres tend to reassume a longitudinal orientation and invade fascia and muscle. Alternatively, (*d*) may be represented by a thin strand of tissues uniting the central with the peripheral stump. A " typical " neuroma of section is illustrated by Fig. 3, and some of the essential features in its anatomy appear in examples of injection with ineffective reagents (see below).

For a proper understanding of the mechanism of inhibition, two points deserve emphasis. The first is that the greater part of the neuroma (unlike the glioma of the peripheral stump) forms within the nerve, i.e. within the compass of the original

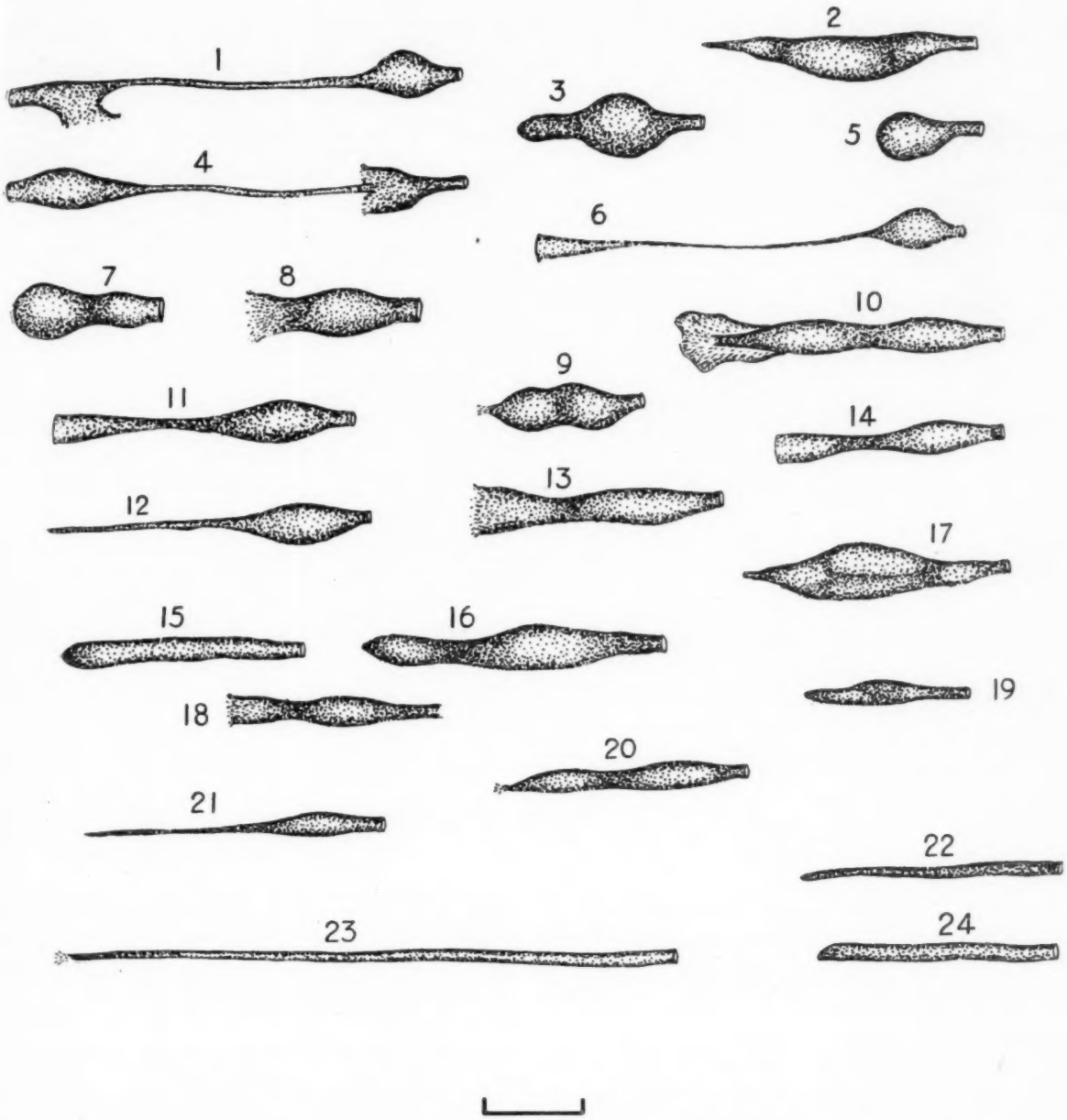


FIG. 2.—Varieties in the conformation of the central stump of the tibial nerve in the rabbit after simple section (1 to 6) and after injection (7 to 24).

In 1, 4, 6, 11, and 14 the central and peripheral stumps have reunited: the central stump lies to the right.

1 to 6: Simple neuromas of section after (1) 200 days (reunion); (2) 389 days; (3) 457 days; (4) 117 days (reunion); (5) 103 days; (6) 165 days (reunion).

(7) 58 days after the injection of heptyl aldehyde; (8) second neuroma formed 179 days after the removal of 7; (9) 109 days after the injection of heptyl aldehyde (another specimen); (10) 330 days after the injection of crotonaldehyde: heavy muscle adhesions at the tip; (11) 61 days after the injection of 10 per cent. uranium nitrate: the stumps reunited; (12) 462 days after the injection of 10 per cent. formaldehyde; (13) 493 days after the injection of 2 per cent. osmic acid; (14) 62 days after the injection of 4 per cent. sodium taurocholate in absolute alcohol: a short resection gap bridged; (15) 60 days after the injection of a saturated solution of iodine in absolute alcohol: an even terminal swelling; (16) 95 days after the injection of a 4 per cent. solution of sodium taurocholate in absolute alcohol; (17) 169 days after the injection of 2 per cent. tannic acid in absolute alcohol; (18) 97 days after the injection of absolute alcohol; (19) 124 days after the injection of sodium phenate (10 per cent. phenol); (20) 207 days after the injection of a saturated aqueous solution of picric acid; (21) 121 days after the injection of a saturated aqueous solution of mercuric chloride: a small bulb has formed above the tapering stretch, which does not represent new outgrowth; (22) 259 days after the injection of 40 per cent. formaldehyde; (23) 237 days after the injection of 1 per cent. gentian violet; (24) 55 days after the injection of 2 per cent. tannic acid in 40 per cent. formaldehyde: the last 15 mm. consists of fixed and dead nerve uninvaded by new fibres.

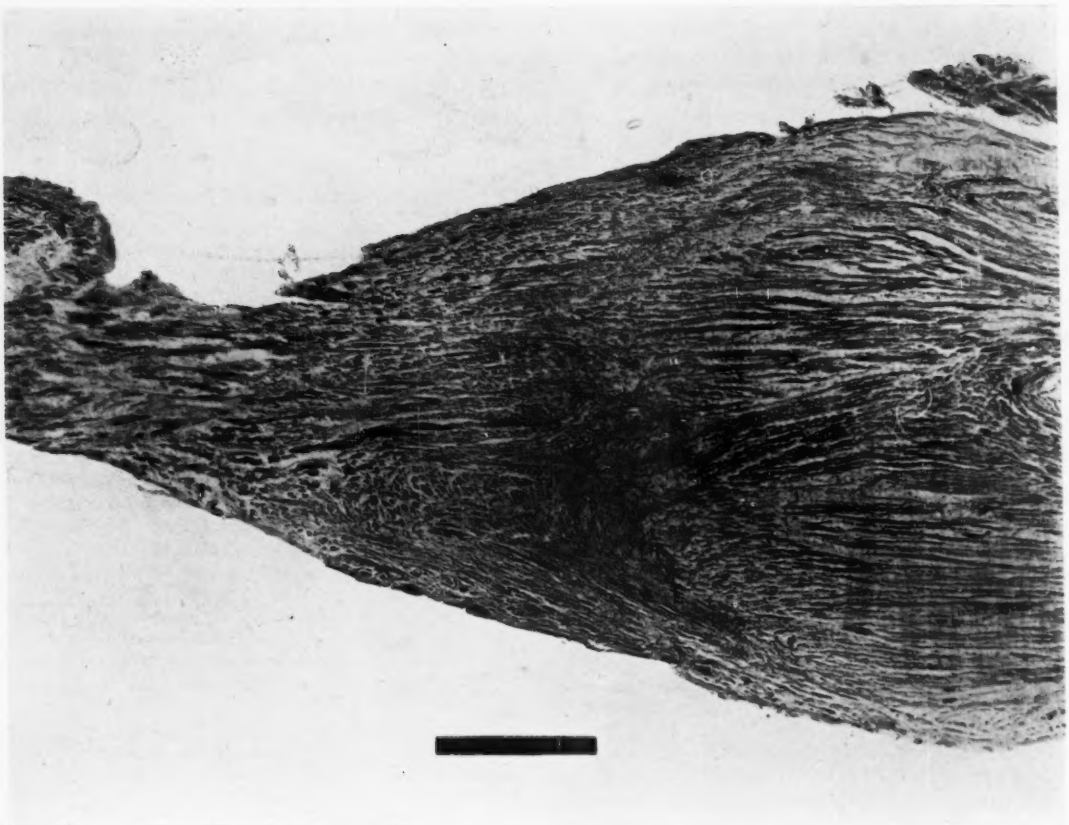


FIG. 3.—The distal half of a 457-day neuroma of section: scale 1 mm., Holmes' stain. The central end lies to the right. Note the abrupt transition between the "flare" and plexiform zones. Beyond the plexiform zone, a comparatively small number of fibres have readopted a parallel orientation and invaded fascia and muscle.

epineurial sleeve, and not by the proliferation of cells which have grown out from the end. This is one of the reasons why the mere closure of the central stump, whether by chemical or surgical means, is inadequate. The second is that as a general rule the end of the neuroma is anatomically speaking open, i.e. the epineurium does not form a complete investment for it. Encapsulated neuromas in the rabbit are rare. The state of the central stump, whether closed or open, is one of the grounds used below for distinguishing between successful and unsuccessful inhibitions.

Chemical inhibitions: Full records are available for 87 experiments, which are divided up as follows :

Alcohol, 70 *to* 100 *per cent.:* 12 experiments, 45 to 189 days, *including* experiments in which alcohol was used as a solvent for sodium taurocholate and tannic acid (Fig. 2, **14, 16, 17, 18**).

Alcohol has been a failure in our experiments. In 5 out of the 12 experiments (cf. Fig. 2, **14**) short resection gaps had been bridged by nerve fibres. All twelve show central swellings of various sizes—smaller where reunion had taken place between the stumps. Heavy adhesions between the central stump and underlying fascia and muscle were the rule. Traces of fixed and unremoved debris have been found in the nerve after three months. In the formation of a bulb, the open state of the central stump, the existence of a plexiform zone and a zone of involvement, the long-period alcohol neuroma closely resembles and cannot be distinguished with certainty from a normal neuroma of section.

It seems justifiable to attribute the greater success of alcohol injection in Huber and Lewis's 28 experiments (11 to 157 days) to the fact that they used multiple injections, often widely separated on the nerve, and that a much greater length of nerve was therefore destroyed. Although the technique of multiple injection might very well be used in clinical practice, our experiments show quite clearly that under uniform conditions, using single-point injections of not more than 0·2 ml. of each reagent, alcohol is notably less successful than the other coagulants we have used. It is noteworthy that in the last four (62 to 137 days) of Huber's 12 additional experiments in which the nerve was left uncut after injection with alcohol, fibres were found to have passed through the coagulated stretch and entered the peripheral stretch of the nerve.

Tannic acid, 2 *to* 4 *per cent.:* Aqueous and alcoholic solutions, 11 experiments, 29 to 189 days (Fig. 2, **17**, Fig. 8, **1, 2**).

Short resection gaps were bridged in 3 experiments, and in these neuromas, though present, were comparatively small. Large neuromas (three or more times the diameter of the normal nerve) were found in 6 cases; and in these 9 taken together, the stumps were heavily involved in fascia and muscle. Two short-period animals (31, 33 days) showed a temporarily successful inhibition, and histological examination showed that the end of the nerve was sealed off with a fixed plug (Fig. 8, **1, 2**) into which new fibres had not yet penetrated. In other experiments there was no evidence that the nerve had been completely impregnated with tannic acid. This fact is referred to again below.

Formaldehyde, 10 *to* 40 *per cent.:* 21 experiments

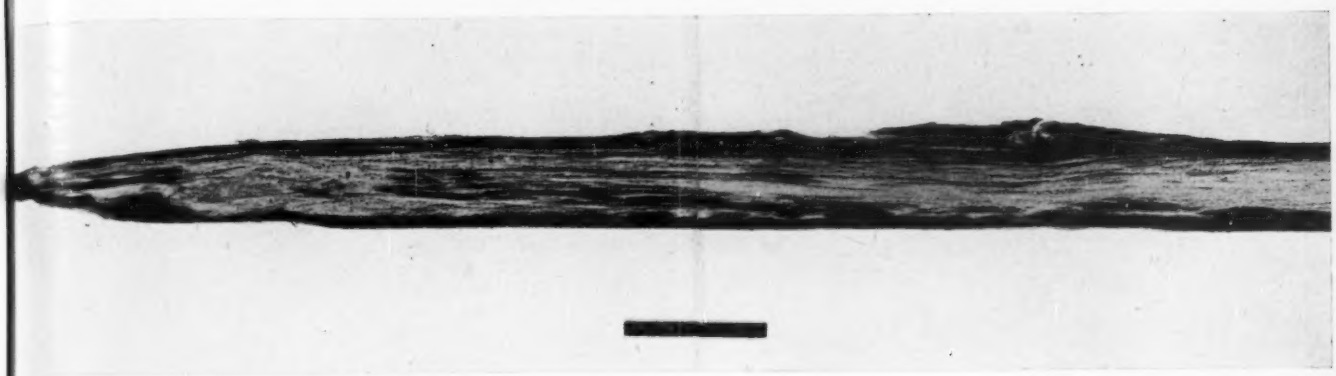


FIG. 4.—About 8 months after the subepineurial injection of 40 per cent. formaldehyde: scale 1 mm., Bodian's stain. The ground plan is similar to that illustrated in Fig. 5, but should be contrasted with that illustrated in Fig. 6. Note that the stump is closed by its epineurial sheath, which is lightly adherent to fascia. No fibres escape.

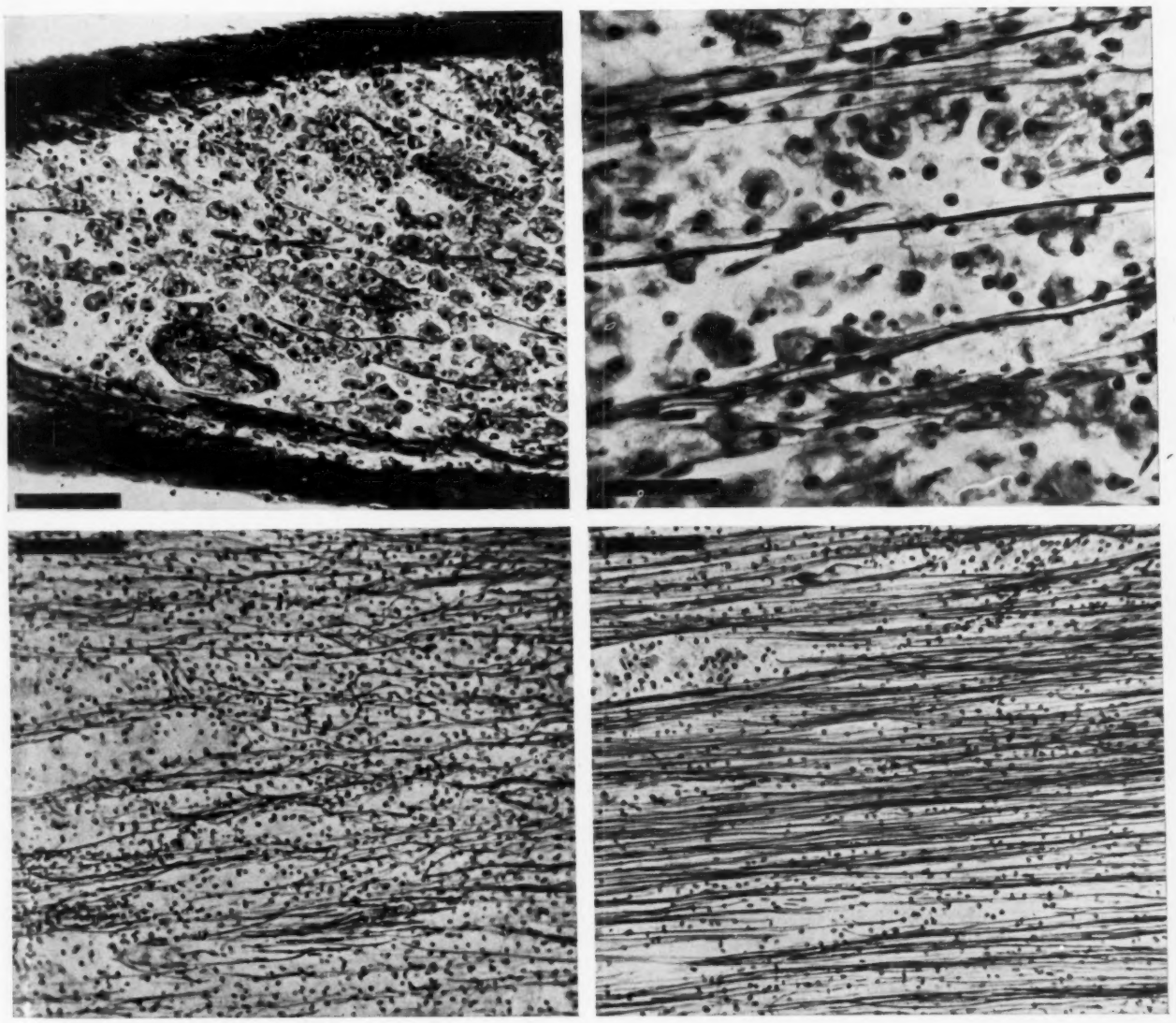


FIG. 5.—Illustrating the general anatomy of the central stump about 3 months after injection with 40 per cent. formaldehyde: Bodian's stain. (1) Scale 0·1 mm. Just behind the tip. A few fibres have penetrated into a dense collection of giant macrophages. (2) Scale 0·05 mm. In the zone of (1), under higher power. (3) Scale 0·1 mm. About 10 mm. behind the tip: zone of fibre deviation. (4) Scale 0·1 mm. About 20 mm. behind the tip: macrophages still abundant.

29 to 462 days. (Fig. 2, **12, 22, 24**; Fig. 4, 5, 6.) These are divided up as follows:

10 *per cent.:* 5 experiments, 68 to 462 days. Resection gaps bridged in two cases. All 5 show bulbous enlargements of the central stump with moderate adhesions.

20 *per cent.*: 3 experiments, 72, 297, 356 days; *40 per cent.*: 9 experiments, 29 to 335 days; *40 per cent. in 5 per cent. tannic acid:* 4 experiments, 29 to 84 days. Experiments of this second group may be considered together. Single point injections of 20 to 40 per cent. formaldehyde have proved strikingly successful. No bulbs are formed. The nerve, which is yellow and lacks its usual sheen, tapers down from its normal width for a length of 30 mm. to a tip lightly adherent to underlying fascia (Fig. 4). Elsewhere the nerve is wholly non-adherent and may be picked up freely from its fascial bed. There is no fibrosis, either in the nerve or in surrounding tissues. Histological examination shows a clear-cut distinction between subepineurial and intraneural injection. In the former case, to which the remarks made above apply, the yellow tapering stretch is found to contain nerve fibres which thread their way through a mass of giant mononuclear cells supported by an extremely sparse stroma of connective tissue. Fig. 5, **1** to **4**, illustrates three zones in a relatively short period (3 months) injection with 40 per cent. formaldehyde: a central zone of normal fibres orientated parallel to one another (**4**); a branching zone (**3**); and a zone of decreasing fibre density (**1, 2**) where the majority of phagocytes are accumulated. The condition is not substantially different after 8 months (Fig. 4), though macrophages are somewhat fewer. There is no swelling of the nerve, and no evidence of adhesion except at the extreme tip. The stump is closed by its own epineurial sheath.

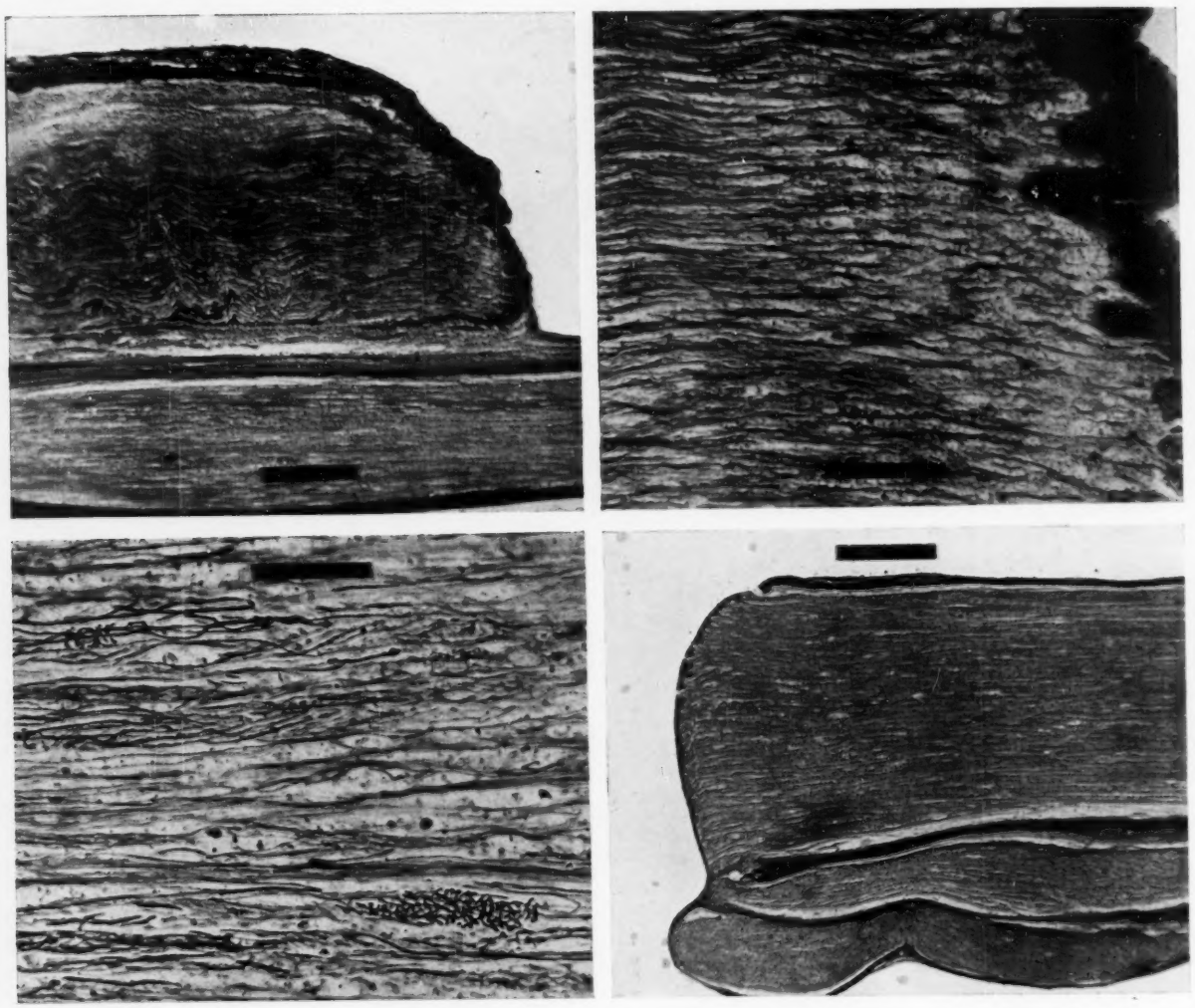


FIG. 6.—Illustrating the general anatomy of the central stump 2 to 3 months after the *intraneural* injection of 40 per cent. formaldehyde. Contrast with Fig. 5. Bodian's stain. (1) Approximately 2 months after injection: scale 0·5 mm. The last 15 mm. of the nerve is fixed and dead, though the epineurial sheath has closed over the tip. The peroneal nerve, running alongside, has been damaged but not destroyed by the injection. (2) Scale 0·1 mm.: the tip, more highly magnified. Fixed and empty remains of the original endoneurial scaffolding. (3) About 15 mm. behind the tip: scale 0·1 mm. The most advanced zone of new fibres in the dead tissue: deviation and spiralling. (4) About 3 months after intraneural injection: another specimen, scale 0·5 mm. Note the abrupt termination of the nerve.

After *intraneural* injection, the histological picture (Fig. 6, **1** to **4**) is somewhat different. The nerve ends off abruptly with a fixed plug (**1, 2, 4**) towards the central end of which (**3**) macrophages are in action and fibres are beginning to invade the dead tissue. Unfortunately, we have no long period experiments with intraneural injection.

Gentian violet,* 1 *per cent. aqueous:* 2 experiments,

* The name given to an ill-defined mixture of the more highly methylated violet pararosaniline dyes (methyl violet, crystal violet, etc.). It may be assumed that *triple-dye* (gentian viloet, acriflavine, brilliant green mixture) would give results comparable to those obtained with gentian violet.

217 and 237 days. Subepineurial injection (Fig. 2, **23**; Fig. 7).

The nerves tapered down from their normal width over distances of 30 and 60 mm. respectively, and were nowhere bulbous or swollen. The last 5 mm. were discoloured with unremoved gentian violet, and there were in each case light attachments at the tip. Longitudinal sections of the longer-period specimen showed extensive accumulations of giant phagocytes at the tip (Fig. 7), the last 10 mm. being collagenized and feebly penetrated by isolated new nerve fibres. It is not possible to say with certainty whether the greater part of the collagen at the tip represents fixed remains from the original injection, or whether it is collagen of new formation.

Higher up, the nerve fibres are clearly threading their way through the remains of fixed endoneurial scaffolding. The material has the appearance of normal regenerating nerve only about 30 mm. from the tip, and macrophage islands are present at least 60 mm. from the tip.

Other coagulants: Chromic acid (1 per cent.), mercuric chloride (sat. aq. soln.), sodium phenate (in the form of the proprietary preparation "phenoda," containing 10 per cent. phenol as phenate), picric acid (sat. aq. soln.), iodine (5 per cent. absolute alcohol), and uranium nitrate (10 per cent. aqueous) together account for 20 experiments ranging in length from 23 to over 500 days. (Fig. **2**, **13**, **15**, **19**, **20**, **21**; Fig. 8, **3**, **4**).

All give results inferior to formaldehyde and gentian violet, though the data for chromic acid (2 experiments: 36 and 119 days) are incomplete. Iodine and uranium nitrate inhibit only temporarily, but picric acid, sodium phenate, osmium tetroxide and in particular mercuric chloride may be said to give marked and significant inhibition for periods up to 150 days.

The single medium period (119 days) chromic acid injected nerve was found to be soft and "puffy" in appearance, and of normal width down to an abrupt pencil-point termination. On microscopical examination (Fig. 8, **3**) the terminal stretch was found to consist of a plug of fixed tissue into which fibres had not penetrated and in which phagocytosis by giant cells had hardly begun. These facts are discussed below.

Non-fixatives: Twenty-two experiments ranging from 29 to 539 days are divided among quinine hydrochloride (1 per cent.), optochin (1 per cent.), antipyrene (5 per cent.), sodium taurocholate (4 to 10 per cent. in absolute alcohol), beryllium nitrate (10 per cent.), crotonaldehyde and heptylaldehyde (10 per cent. in absolute alcohol). (Fig. 2, **7**, **8**, **9**, **10**, **14**, **16**).

As a class, non-fixatives have given uniformly unsuccessful results, and they throw very little light on the mechanism of inhibition. The first three may be regarded as having no significant effect from the point of view of fibre inhibition, while Salm (1940) has shown that quinine elicits a prompt fibroblast reaction shortly after injection. Crotonaldehyde and heptylaldehyde are in no way comparable to formaldehyde; they are unpleasant to handle and give rise to moderate fibrosis and other secondary reactions. Beryllium nitrate is likewise ineffective, while giving rise to a most violent and undesirable fibroblast proliferation.

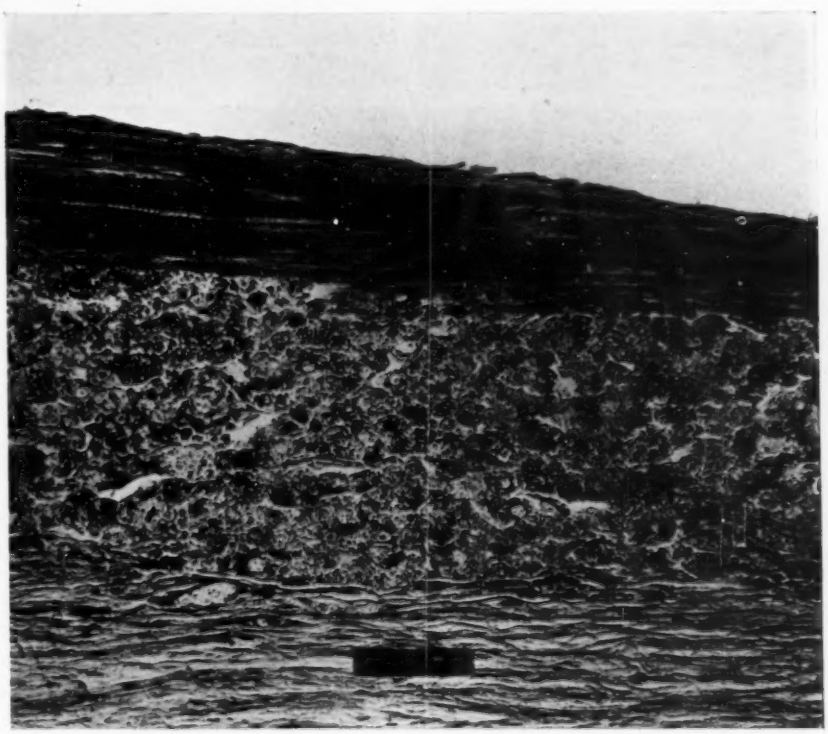


FIG. 7.—15 mm. behind the tip of the nerve 8 months after injection with 1 per cent. gentian violet. Scale 0·075 mm., Bodian's stain. A densely packed collection of macrophages occupies about one-third of the diameter of the nerve in sectional view.

Evaluation of Results

In judging between the efficacy of the various reagents listed above, the question of neuroma formation is clearly not the only one to be considered. Nor, since the experiments range over a considerable period, is it possible merely to record the presence or absence of fibres in the injected stretch. We will leave aside the total failure represented (as in 5 out of 12 experiments with alcohol) by functional reunion of the stumps, since this does not by any means occur invariably in the controls. In the main, the inhibitions described as "successful" (a term which applies to formaldehyde and

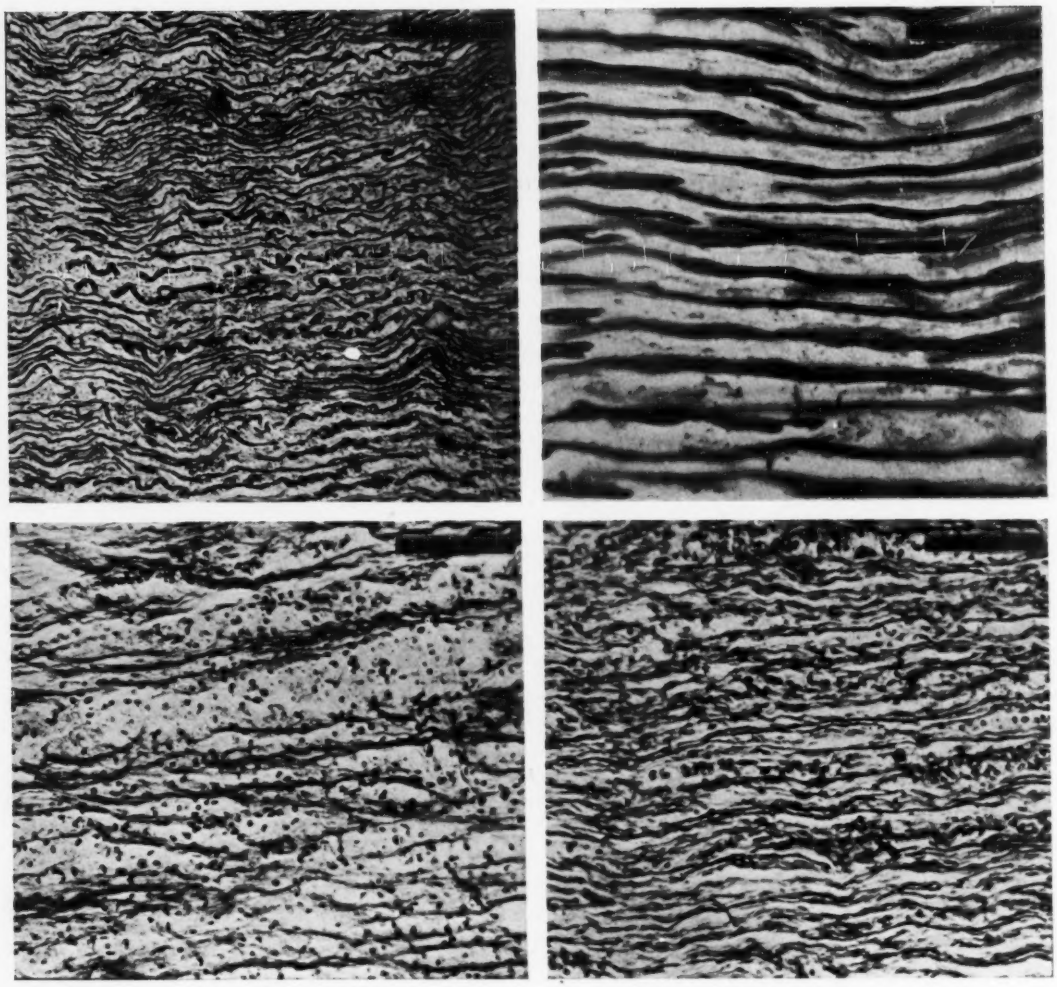


FIG. 8.—The effect of fixation with tannic and chromic acids. Bodian's stain. (1) One month after injection with 4 per cent. tannic acid, just behind the tip of the nerve: scale 0·1 mm. (2) The same: scale 0·05 mm. The axons are fixed and dead: no living element is present. (3) and (4): 4 months after the injection of 1 per cent. chromic acid: scale 0·1 mm. In (3), macrophages are removing the fixed cellular debris just behind the tip of the nerve, but no axons have yet arrived. In (4), 5 mm. behind the tip, regenerating axons are beginning to invade the terminal plug.

gentian violet experiments, and with greater reserve to medium-period experiments with some of the other fixatives) are distinguished from the controls and the simple failures—reagents which failed without giving rise to secondary reactions—in the following combination of ways :

State of the Central Stump

Successful inhibitions	*Failures and controls*
1. Axons *decrease* in number towards the periphery. (This is clearly shown by Figs. 4, 5, and 6. The fact that *some* fibres reach the tip is of secondary importance. They gradually fall off in number until only one or two are left.)	Axons *increase* in number towards the periphery, as a result of branching and convolution.
2. Absence of all but trivial and superficial adhesions; *closure* of the central stump; no escape of fibres.	Heavy and intimate adhesions to fascia and muscle; central stump typically *open;* invasion of neighbouring tissues by nerve fibres.
3. No neuroma: the nerve is equal to or less than its normal width throughout its length.	Neuroma formation *invariably* occurs.
4. No gross fibre-bundle deviations, "flaring," convolution and other signs of unrestricted free growth.	Flaring, whorling and convolution of fibre bundles to form a felt-like plexus.
5. Endoneurial connective tissue reaction lacking.	Proliferation of endoneurial connective tissue.

If these criteria are applied to the experimental results, as they have been above, they clearly distinguish formaldehyde and gentian violet from the other fixatives ; and fixatives as a class from non-fixatives.

The Theory of Inhibition by Coagulants

The case of alcohol is simplest and will be considered first. Coagulation by alcohol, like that brought about by heat, is thought to consist essentially of dehydration of the colloidal particles without secondary reactions. Alcohol fixed proteins are in

no way resistant to proteolytic digestion; moreover alcohol is not only a most feeble penetrant of tissue (Underhill, 1932; Medawar, 1941a) owing to its high fixing concentration, but any excess of it that remains will be rapidly metabolized away. It follows that alcohol destroys nerve without offering much more than a temporary *mechanical* obstacle to regenerating fibres. There is no theoretical reason why it should be a particularly effective inhibitor, and in fact it is not.

Tannic acid, chromic acid, and gentian violet share in common the property of making the proteins they fix totally resistant to tryptic digestion (Medawar, 1942), and the first two at least, for which further data are now available, likewise stabilize proteins to digestion with papain, which, like the tissue cathepsins, acts in a faintly acid environment. They therefore offer a chemical as well as a mechanical obstacle to axon regeneration.* Examples of tannic acid and chromic acid fixation (Fig. 8) show that highly resistant chemical seals can be formed by their action. Unfortunately, tannic acid penetrates tissue so feebly (see Medawar, 1942) that it is most unlikely that the whole thickness of the larger human nerves could be coagulated by it. Even the failure of tannic acid fixation of the tibial nerve of the rabbit seems to be due in part to incomplete fixation. But it is not by any means certain that the formation of a mechanically perfect seal at the end of the nerve is a desirable reaction. Experiments on ligation (for this treatment amounts to chemical ligation) and encapsulation of the central stump with collodion sheaths show that neuromas are not prevented from forming, whether fibres can just squeeze their way out or not.

The evolution of formaldehyde-fixed central stumps appears to fall into the following stages : a latent period, the presence of which we can take for granted ; the slow mobilization of giant mononuclear phagocytes to break down the coagulated tissue ; the invasion of the fixed tissue with axons, probably at first outstripping their Schwann cells; and finally—a stage which has not been reached in practice—the complete colonization of the stump with myelinated fibres. The invasion process, which is well under way before 100 days (Fig. 5) is by no means complete at 300 (Fig. 4) ; and the inference is that the inhibited stretch is permeable to fibres but highly unfavourable to their growth. Why formaldehyde should be so successful is not clear. It is not a precipitant, and fixation by it does not interfere with subsequent proteolytic digestion. It is however a most powerfully reactive substance, which condenses with a great variety of compounds other than proteins, and it is quite possible that its action on nerves is due to properties other than those of mere protein fixation.

The action of gentian violet is easier to understand. In the absence of a circulation at the end of the central stump, the conditions there may be likened to a supravital tissue culture. Gentian violet is strongly "adsorbed" on to living tissues, and under *in vitro* conditions is an intensely powerful protoplasmic poison.* It is liberated in its original form extremely slowly (e.g. gentian violet precipitated proteins will still colour standing water after more than 2,000 hours continuous washing), and the proteins themselves are totally resistant to digestion by tryptic-type enzymes (Medawar, 1942). Since traces of gentian violet have been found in injected stumps after more than 200 days, we may assume that it is still acting as an inhibitor at that period. Gentian violet has the advantage of being highly coloured ; and in clinical practice its antiseptic action could be extended to gram negative organisms by combining it with acriflavine and brilliant green in the form of the mixture known as *triple-dye*.

Coagulation by the other reagents listed above, and more particularly by the salts of heavy metals, need not be considered in detail, though it throws a clear light on the mechanism of inhibition. The proteins they fix are not resistant to proteolysis, but the highly toxic heavy metal ion is probably liberated during digestion. Whatever success they have in practice cannot therefore be attributed merely to killing the central stump of the nerve and plugging it up. It must be due, to a far greater extent, to the steady maintenance of an environment which is permeable, but only just permeable, to regenerating fibres. The reaction is one of chemical defence in depth.

Fibre-inhibition, neuroma formation, and adhesions

The ligation experiments described earlier in the paper, and the qualitative observation that neuromas of section tend to be smaller where a thick functional bridge is established between the stumps, suggest that neuroma formation, although it *might* be an independent traumatic reaction on the part of Schwann and connective tissue elements in the nerve, does in fact depend upon the presence of downgrowing axons. This conclusion is exactly confirmed by the experiments on chemical inhibition reported above. When fibres are absent, or merely penetrate in small numbers to the tip, no neuroma is formed. For this reason the presence or absence of bulbs may be used as an index of the success of inhibition.

A much less obvious consequence of fibre inhibition is that the heavy and intimate adhesions between the central stump of the nerve and neighbouring tissues which are invariably found in control experiments and after ineffective inhibitions are wholly lacking in the "successful" inhibitions. Here again, there is no very obvious reason why adhesions should not be set up by the connective tissue elements in the nerve ; but this proves not to be the case. Where fibres are absent or present in trivially small numbers in the inhibited stretch, adhesions are likewise lacking, or are confined to

* It should be noted that the polymorphs and lymphocytes of the rabbit lack tryptic-type enzymes (Barnes, 1940) and the giant cells referred to in the text may do so as well.

* Tests by the methods of Jacoby, Medawar and Willmer (1941), section II, and Medawar (1941b) give gentian violet a "threshold" toxicity to fibroblasts below 1: 100,000.

a light epineurial attachment at the tip of the nerve. Elsewhere, the nerve disengages freely from its fascial bed. There has been no exception to the rule that where no neuroma is formed, adhesions are superficial or absent.

Clinical Application

Injection with coagulants destroys a relatively greater length of nerve in laboratory animals than it does in men. The absolute length is however more important, if the reasoning of a previous section is correct ; so that the experimental findings can be translated into clinical terms without undue reserve. It is most unlikely that human nerves behave much differently from those of the rabbit with regard to such an unspecific procedure as chemical coagulation.

Experience in injecting the nerves of the rabbit suggests that for the best results the following details should be observed :

(*a*) The nerve should be carefully packed with moist absorbent gauze before injection.

(*b*) Injection should be both intraneural and subepineurial.

(*c*) Steps should be taken to control the distance the injection fluid travels up the nerve. The injection fluid should be coloured ; with methylene blue in the case of formaldehyde. A light ligature some centimetres below the lowest working branch of the nerve, later removed, should prevent the injection fluid travelling further up than is intended.

(*d*) Since there must always be the danger of a leak from the nerve after injection, it should be replaced where it can do little harm, and in no case in contact with another nerve.

Indications and contraindications for the use of injection methods naturally fall outside the scope of this paper. But whatever reasoning justifies the removal of a neuroma for the attempted relief of pain likewise justifies the prophylactic use of injection in order to prevent it forming again. We conclude from these experiments that formaldehyde (20 to 40 per cent.) and gentian violet (1 per cent.) are suitable reagents for this purpose, while alcohol, which has hitherto been so widely used, is relatively ineffective. It should not be forgotten, however, that both formaldehyde and gentian violet are intensely poisonous substances ; and we do not suggest that they should replace alcohol for delicate injections, such as those of the Gasserian ganglion, where even the use of alcohol is attended with sufficient danger.

Summary

1. Chemical and surgical methods for preventing the regenerative growth of nerve fibres from the central stump of a divided nerve are discussed and reviewed.

2. An attempt has been made to evaluate chemical methods of inhibition by a uniform series of injections of fixatives and non-fixatives into the tibial nerve of the rabbit.

3. Fixatives as a class are superior to non-fixatives. Formaldehyde, in concentrations of 20 per cent. upwards, and 1 per cent. gentian violet prevent the formation of end-bulbs and the development of adhesions between the nerve and its bed for at least a year. Alcohol is only effective for periods below two months. Other fixatives occupy an intermediate position.

4. Neuroma formation and the development of strong adhesions between the stump of the nerve and its bed do not occur in the absence of regenerating nerve fibres.

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FATAL INTRACRANIAL VENOUS HÆMATOMA FOLLOWING VENTRICULAR DRAINAGE *

BY

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(RECEIVED 7TH AUGUST, 1942)

A FATAL complication occurring in the course of a routine procedure must needs be placed on record, and although the title of the present communication contains the gist of the story, the full records of the incidents supply a theoretical interest which equals their practical importance. The three case histories which follow are concerned with the development of clots, extradural in two, intradural and intracerebral in one case, and rapidly fatal in all three. The clots might have been dealt with successfully had they been recognized in time in the second and third instances. It is evident that the speed of production of the clot is of no little importance, and it may well be that once the possibility of the condition is better recognized, successfully treated cases may in the future be placed upon record.

Extradural Hæmorrhages after Lowering Intracranial Pressure (2 cases)

Case 1.—D. R., a schoolgirl aged fourteen, was admitted to the Manchester Royal Infirmary under the care of Professor Jefferson, on the 12/2/40. For the past four years she had suffered from attacks of severe occipital headache accompanied by bouts of vomiting. The first of these attacks, according to her mother, followed a trivial head injury. During the six months preceding her admission to hospital the headache had become more frequent, she had walked unsteadily, and on occasions had experienced attacks in which " things seemed to spin " in front of her eyes. She had fallen in these attacks, but had never lost consciousness. Urgency of micturition was her only other complaint.

Examination showed her to be a well-developed girl, mentally alert and in a good state of general health. A medium degree of chronic œdema without hæmorrhages affected both optic nerve-heads. The visual fields showed no significant alteration other than enlargement of the blind spots, visual acuity was 6/9 in both eyes, the pupillary reflexes were normal and ocular movements full in all directions. There was no nystagmus. Tone was increased in all limbs with exaggeration of deep reflexes, and the plantar responses though not definitely extensor were undoubtedly abnormal. She performed the usual cerebellar tests well, but walked on a broad base, holding herself stiffly and her head inclined to the right.

X-rays of the skull revealed some increase in the depth of the convolutional markings, flattening of the posterior and shortening of the anterior clinoid processes. Her skull was unusually large, a fact well known to the patient's mother, who for years had experienced difficulty in buying hats for her. The distance between the root of the nose and the external occipital protuberance measured over the vertex was 15½ inches.

The history, clinical state, and X-ray appearances suggested a slowly evolving increased intracranial tension. The absence of crisp signs of a clearly localizing nature and the chronicity of the process argued against the presence of a tumour and the diagnosis most favoured before operation was hydrocephalus due to intermittent obstruction of the iter. This later turned out to be the correct interpretation.

An exploration of the posterior fossa without previous ventriculography was carried out on the 27/2/40. The operation was performed under intratracheal nitrous oxide-oxygen and under local anæsthesia, supplemented by ¾ the basal anæsthetic dose of avertin. Omnopon gr. ¼ and Scopolamin gr. 1/200 were given two hours before the operation. The patient's breathing did not become distressed under the anæsthetic induction. The first step in the operation was puncture of the left lateral ventricle; the pressure of the cerebrospinal fluid was found to be higher than 400 mm. of water. Very slowly fluid was allowed to escape and the pressure reduced to atmospheric. The brain canula was then replaced by a rubber tube with a fine bore. Through this fluid continued to drip while the muscle was stripped from the occipital bone and the arch of the atlas removed. When the latter stage had been completed and before the occipital bone had been removed or even perforated, there was an unexplained and sudden gush of cerebrospinal fluid from the ventricle; it continued for about a minute and then the flow of fluid ceased. At the same moment small vessels in the muscle began to bleed, larger vessels previously coagulated opened up again, and the wound rapidly filled with dark blood. While still engaged in procuring hæmostasis the surgeon was informed by the anæsthetist that the

* Based on a paper read at the Meeting of the British Neurosurgical Society, July 1941.

patient had stopped breathing and that her systolic pressure had risen from 110 to 150, but her pulse had fallen (Fig. 1). Five minutes later she breathed

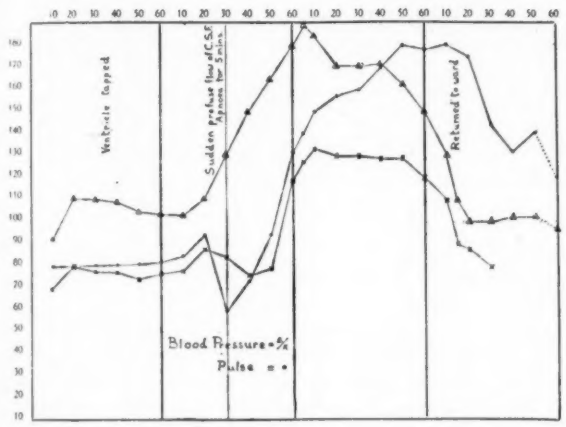


FIG. 1.—Chart of the blood pressure, pulse and respiration in Case 1.

again, but her blood pressure continued to rise, and her pulse rate after a temporary decrease climbed steeply. The occipital bone was rapidly removed, but so great was the tension in the posterior fossa that as soon as the dura had been opened for a distance of about 1 cm. the cerebellum bulged through the opening, bursting its surface vessels. No more fluid could be obtained from the left lateral ventricle; several attempts to locate the right posterior horn failed. Attempts to find a cyst by needling the vermis were unsuccessful; prolongation of the dural incision was impossible owing to the hæmorrhage which followed each attempt. The systolic pressure, having reached a peak of 190 mm., began to fall, though the pulse rate continued to rise until it no longer could be accurately counted. The wound was rapidly closed and the patient returned to the ward. She survived the operation for sixteen hours and during that period her temperature rose to 106°. Two intravenous injections of 50 per cent. sucrose caused no change in her condition.

At the post-mortem examination a large extradural clot was found overlying and compressing both frontal lobes. It extended upwards from near the floor of the anterior fossa to within about a centimetre of the coronal suture. Its maximum thickness was 4 cm. and more blood was present on the right side than the left. The lateral and third ventricles were greatly dilated, and at the level of the anterior quadrigeminal bodies the iter of Sylvius could not be identified. Histological studies later revealed that the lumen of the iter at this level had been replaced by proliferations of astrocytes enclosing narrow channels and extending into the central gray matter. It may be presumed that during the lifetime of the patient these channels allowed the occasional passage of small quantities of cerebrospinal fluid. Tentorial and foraminal herniations were present.

Comment.—The story of the operation, truly a surgical nightmare, the chart with its eloquent graphs of blood pressure and pulse rate, and finally the necropsy findings form a picture which can gain but little in completeness by further comment. The chart brings to mind the results of animal experimentation concerning the effects of raised intracranial tension (Cushing, 1902), but in cases of rapidly expanding intracranial hæmorrhage the rising arterial pressure and the cerebral vasodilatation combining to restore the cerebral circulation, must add pari passu to the volume of the effusion and establish a vicious circle. The combination of supratentorial pressure with infratentorial decompression peculiar to the present case produced tentorial and foraminal herniation, thus further embarrassing vital centres. The greatly increased pressure in the posterior fossa mentioned in the description of the operation has its corollary in the rapid rise of the patient's pulse rate indicating failure of the vagus centre. It is interesting that the diastolic pressure did not for the first thirty minutes follow the upward trend of the systolic pressure, and for the first fifty minutes its curve closely followed that of the pulse rate.

Case 2.—E. P., a girl aged 10 years, was transferred to the Neurosurgical Department on the 31/12/41, having previously been under the care of Dr. F. R. Ferguson. For the past year she had suffered from headache, more severe and accompanied by vomiting in the past six months. Two months ago her sight deteriorated rapidly; she could no longer see the writing on the blackboard, and she ceased to attend school.

She was a well-developed girl in a fair state of nutrition. Her head was enlarged, its greatest circumference measured 23 inches. No gross mental defect was observed, but on some days she was apathetic and unduly sleepy. Both optic discs were affected by secondary atrophy, and she could barely count fingers at a distance of 18 inches. Her visual fields were generally constricted; her eyes moved freely in all directions without nystagmus. When she stood or walked she swayed and stumbled both to the right and left, but when she lay in bed her limbs disclosed no striking dysfunction apart from a slight terminal tremor which affected the movements of both hands.

On the basis of these clinical findings a definite diagnosis could not be made, though it was considered that her condition was more likely to be due to an inflammatory than a neoplastic obstruction of the flow of cerebrospinal fluid from the ventricles. Ventriculography was performed on the 7/11/41, and 110 c.c. of fluid were replaced by air. The films showed gross symmetrical dilatation of the lateral and third ventricles, and only the first three millimetres of the iter were outlined. A fine-bore rubber tube was introduced into the left lateral ventricle to provide a temporary safety valve against any rise in intracranial pressure and the child was returned to the ward. Her condition was good, though she was listless, and when questioned com-

plained of headache. About 1½ hours later the child developed a series of convulsions and became deeply unconscious. She was slightly cyanosed, her pulse rate was 180 and her respirations, peculiarly strained, were at the rate of 40 to 50 per minute. The fits followed each other in rapid succession, sometimes without a pause, and at first they were mainly of a tonic "decerebrate" variety. Each attack began with opisthotonus which lifted the patient's back off the bed; her arms became extended and overpronated, and spasm of the adductor and extensor muscles of the thighs determined the posture of the legs. No change in the attitude of the limbs occurred when the head was passively moved. Later another type of attack was observed: it consisted of loose-jointed flexion and extension movements at the left hip, knee, and elbow reminiscent of hemiballism. Occasionally the patient's eyes slowly moved from side to side and a fine horizontal nystagmus was present. The pupils were dilated and did not react to light. The flow of cerebrospinal fluid from the ventricular drain had ceased, and from the opposite ventricle only a few drops of fluid escaped under pressure.

The fits were first controlled by an ether anæsthetic and later 8 c.c. of a 10-per-cent. solution of sodium pentothal were introduced rectally. No further attacks occurred after this, but she died five hours after the onset of convulsions.

At the post-mortem examination an extradural clot was found overlying both frontal lobes. Its vertical extent from the floor of the anterior fossa was 15 cm., at its centre it was 5 cm. thick, and it measured 11 cm. from side to side. Careful scrutiny of the dura failed to reveal any indication as to a likely source of the bleeding. There were bilateral tentorial and foraminal herniations, and on sectioning the mid-brain the iter was found to be obstructed by a rounded tumour about the size of a cherry. Histologically the tumour was later proved to be an astrocytoma.

Comment.—For 1½ hours after her return to the ward following the ventriculography and institution of ventricular drainage the child was thought to be asleep. The fits first attracted the attention of the nursing staff. It is possible that she had been unconscious for some short time before the onset of the seizures which by their character—decerebrate rigidity and hemiballistic movements—suggested that a lesion had occurred at the level of the mid-brain. This interpretation was anatomically correct, for the herniated temporal lobes compressed the mid-brain. Jefferson (1921) for the first time described decerebration occurring in extradural hæmorrhage and in a more recent paper (1938) explained how tentorial herniation may bring about decerebrate rigidity.

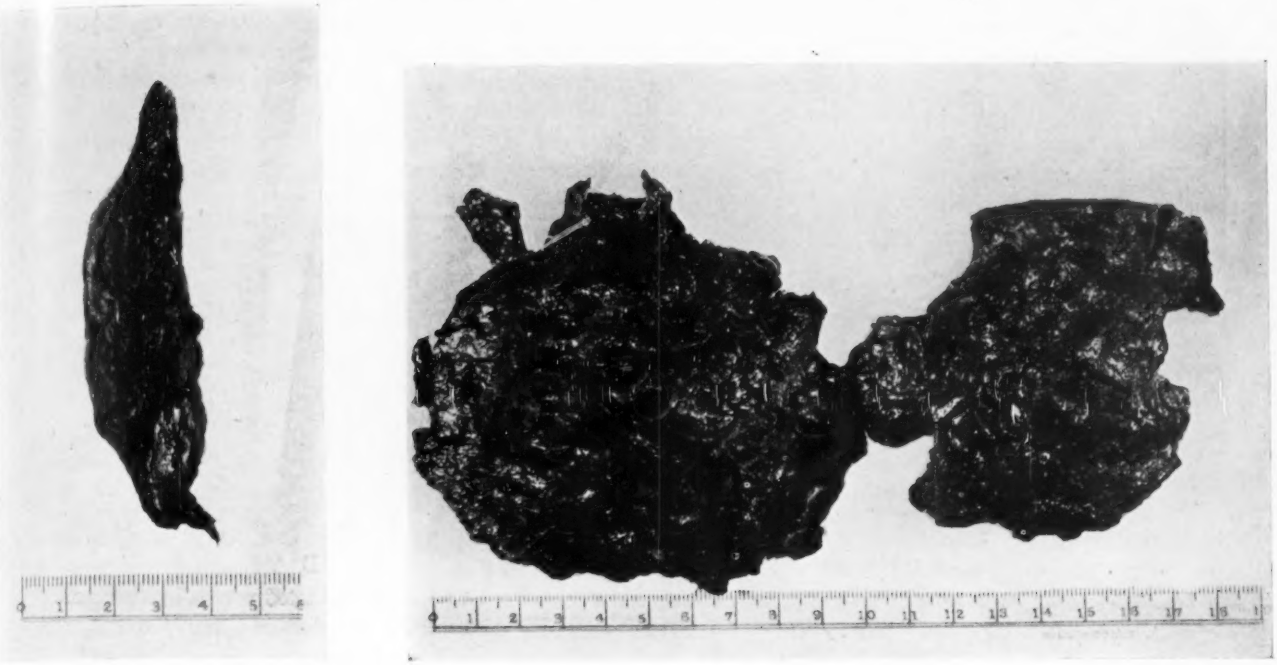
Subdural and Intracerebral Hæmorrhage after Lowering Intracranial Pressure (1 Case)

Case 3.—A. B., female aged 24 years, was referred to Professor Jefferson on the 13/4/42. Excruciating headache and unsteadiness had troubled this patient for four months before her admission. The headache affected the sides and back of her head and radiated into the neck, making all head movements painful. On four occasions her legs had given way, she had fallen, but had not lost consciousness nor been dizzy. On each occasion she got up almost at once and walked on. During the month before her admission the headache had become much more severe. Temporary loss of vision accompanied some of the attacks of pain. Her vision had deteriorated so that she no longer could read ordinary small print, and she had experienced double vision.

She gave this history readily though her statements regarding significant dates were not reliable. Both optic discs were swollen and there were scattered retinal hæmorrhages. The right external rectus was completely and the left partially paralysed. Ocular movements in all other directions were normal and there was no nystagmus. Her pupils reacted briskly to light and on convergence. Examination of her arms and legs yielded little positive information. The left hand was a trifle less steady than the right, and in performing the "heel-knee" test she overshot the mark a little with both heels. The tendon reflexes were depressed in all four limbs, but both plantar responses were extensor. The presumptive diagnosis was hydrocephalus due to cerebellar cyst.

On the day following her admission a fine-bore rubber tube was inserted into the posterior horn of the lateral ventricle because of the severity of her headache; the ventricular pressure was 200 mm. In the afternoon of that day she felt much better, but in the evening her head was retracted and she called out, apparently in great pain. The next morning she complained of severe frontal headache and screamed with pain every few minutes. She had difficulty in finding the words to convey even a simple statement. Her lips were slightly cyanosed; her pupils were equal and reacted to light, but her neurological state had not otherwise altered. No more C. S. F. escaped from the drain. Her temperature was 101·2°, her pulse rate 76. About an hour after this examination she suddenly stopped breathing. Artificial respiration was instituted at once and continued until her circulation failed five hours later.

At post-mortem both the right and left frontal lobes were covered and compressed by subdural blood clots, the one on the left being the larger (Fig. 2). In addition an intracerebral hæmorrhage into the white matter of the left occipital lobe had occurred in the track of the ventricular drain (Fig. 3). There was slight tentorial herniation on the left, but no foraminal prolapse. All four ventricles and the iter were greatly enlarged, and the foramen of Magendie appeared to be occluded by a membrane of thickened pia-arachnoid. To the naked eye the basal arachnoid throughout appeared tougher and more opaque than is normal, but microscopy failed to reveal inflammatory changes in the lepto-meninges. Histological sections of the brain area adjacent to the intracerebral hæmorrhage



A B

FIG. 2.—The subdural clots from Case 3 photographed after formalin fixation. The larger clot was on the left side.

showed intense hyperæmia of all vessels, many of which were surrounded by hæmorrhages. These changes were most marked in the white matter although cortical and surface vessels were also affected (Fig. 4). In the mid-brain only an occasional hæmorrhage was seen and the state of filling of the vessels was not excessive.

Comment.—In this case ventricular drainage was performed as an emergency measure in the hope that it might improve the patient's condition sufficiently to allow an operation to be undertaken after a day or two and to relieve the patient's headache. After a temporary improvement the headache returned in its former intensity, and shortly before the patient lost consciousness dysphasia was observed as the only additional neurological abnormality. Its significance did not sufficiently impress itself on the observers because it was not very obtrusive in so ill a patient who soon lost consciousness. She was thought to have a posterior

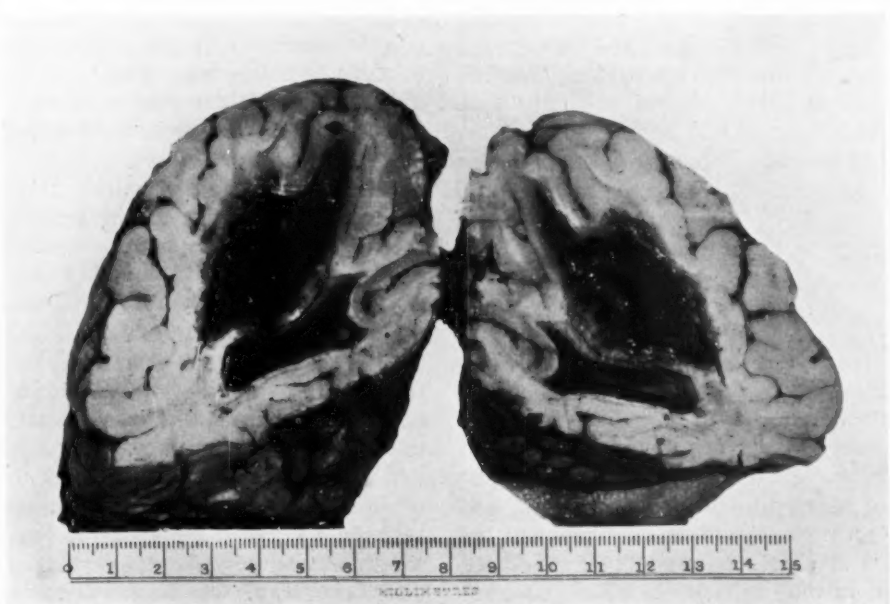
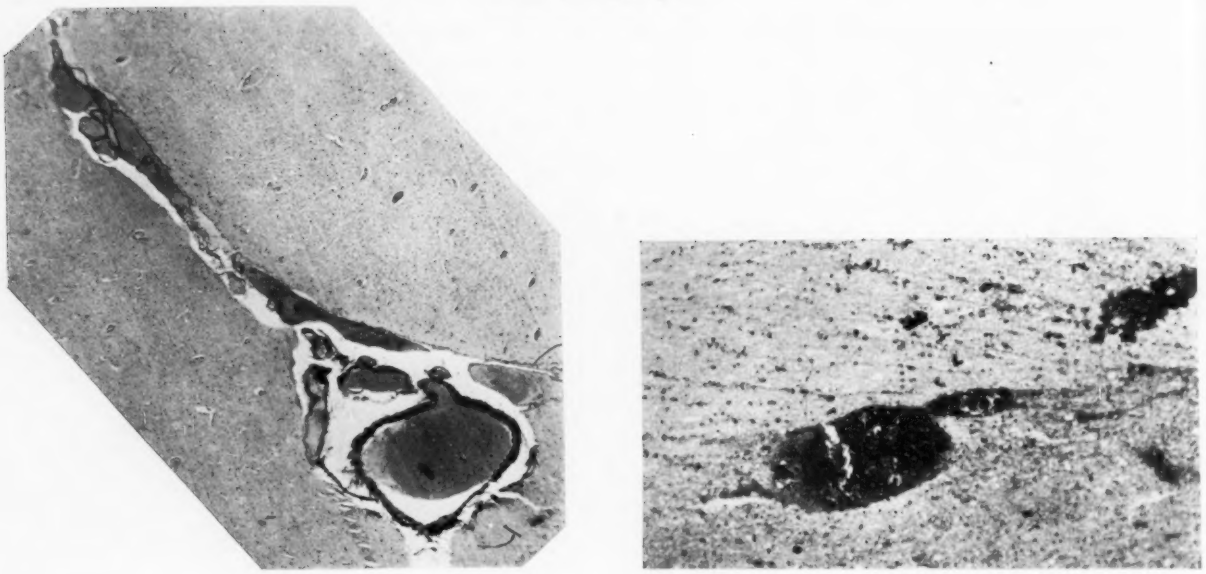


FIG. 3.—Section through the left occipital lobe from Case 3. Note that smaller hæmorrhages have occurred near the ventricle and elsewhere in the white matter.

L



A B

FIG. 4.—Photomicrographs of sections through left parietal lobe from Case 3. (*a*) Dilated vessels in a sulcus. (*b*) Perivascular hæmorrhages in white matter.

fossa cyst and worsening of her condition was clinically attributed to a change in the tumour or in its neighbourhood. No striking circulatory changes were recorded in this patient, but her pulse rate—76—was relatively slow when her temperature had risen to 101·2°.

The three patients whose stories have been told died from intracranial hæmorrhage following ventricular drainage. Internal hydrocephalus with raised intracranial tension was present in all three; two had an obstruction of the iter near its commencement, in the third patient there was adhesive arachnoiditis at the foramen of Magendie. The hæmorrhage was extradural in two cases, subdural and intracerebral in Case 3. Although the vessels responsible for the hæmorrhage could not be identified, the situation of the clots and the absence of arterial disease or injury made it likely that the bleeding was venous. The extradural clots were probably derived from a number of dural veins, the subdural hæmorrhage from the rupture of a vein which crossed the subdural space on its way to the longitudinal sinus. All three extracerebral clots overlay and compressed the frontal lobes.

Discussion

Ventricular taps to reduce intracranial pressure during operations designed for posterior fossa lesions was introduced by Cushing and has greatly added to the safety with which many neurosurgical operations may be carried out. Following a suggestion by J. R. Learmorth, ventricular drainage was extended into an operation in its own rights at the Mayo Clinic, and E. R. Schmidt (1938) reported 24 cases in whom the ventricles had been continuously drained for periods up to 79 days. Only nine of these patients survived eventually, but since it may be assumed that either the pathology of the lesion or the patients' general state precluded an attempt at a radical cure, the high mortality rate does not disparage the value of the method in a selected group of cases. As a method of rapid and prolonged decompression it is attractive for tiding a patient over an acute phase and for making bad cases more fit for operation. It is especially attractive after ventriculography if a general anæsthetic is to be given. An indwelling drain relieves the patient of the possibility of an acute pressure catastrophe during the stage of induction when anoxæmia and hypercapnia may introduce cerebral circulatory difficulties that would excite a fatal mid-brain hæmorrhage undetected at the time and credited to the operation itself in the after-event.

In this clinic the method has been extensively employed without ill effects until the present series of fatalities occurred. These have naturally prejudiced us against the method, but possibly we have recently been using too wide a bore tube. The introduction of a ureteric catheter was originally advocated, but the difficulties of rendering gum-elastic material sterile caused us to change over to the use of a fine-bore rubber tube. Its end should be half closed with a stitch so that fluid just drips slowly from the opening. We have not always done that; it was not done in Case 3.

The first time an extradural clot occurred it was thought to be ill-fortune, but when two further cases made their appearance it was clear that these hæmorrhages were something important. It is not difficult to trace a number of factors which could cause intracranial hæmorrhages when hydrocephalic ventricles are drained, but it is puzzling to understand why the employment of the method under entirely similar circumstances in the past did not more frequently result in this complication.

The obvious mechanical effect of ventricular drainage is twofold: reduction of intracranial

pressure and diminution of the volume of cerebrospinal fluid. As the intracranial pressure falls the dura, no longer subjected to tension, may contract by its elasticity and in some places become detached from the bone. Traction exerted on the dura via the venous anchorage of the brain presumably aids this process with the result that veins passing between the membrane and the skull are torn. The initiation of extradural clots may therefore depend on the ease with which the dura strips from the bone and on the original degree of ventricular dilatation; their incidence should be highest in the young in whom cerebellar tumours, strictures of the iter and adhesive arachnoiditis are common causes of very complete ventricular blocks and in whom the dura is loosely attached.

The emptying of the ventricles must affect the venous circulation, for the venous and cerebrospinal fluid pressures are closely related and an alteration in the one produces a corresponding change in the same direction in the other (Hill, 1896; Weed and Hughson, 1921). Thus ventricular drainage will cause the venous pressure to fall and, as the volume of cerebrospinal fluid decreases, blood will be retained in the intracranial veins. Fig. 4 demonstrates the hyperæmia which may occur under these circumstances. Possibly veins that have for long been compressed by increased intracranial tension have suffered anoxæmic damage and their walls may not be equal to the strain now imposed on them. The greatest burden may fall on the veins which connect the dural sinuses with the brain, for they are not supported by parenchyma and are dragged on as the ventricles empty. Once a vein has ruptured a clot will form and expand as long as the venous pressure exceeds the cerebrospinal fluid tension (Wegefarth, 1914). This condition is fulfilled in ventricular drainage. Presumably after a single tap the cerebrospinal fluid pressure soon rises again, thus preventing extensive separation of the dura and the formation of a hæmatoma, but should the pressure remain low a clot could result from one ventricular tap. Similarly intracerebral hæmorrhage in the track of the canula, as occurred in Case 3, might follow a single ventricular puncture if the cerebrospinal fluid pressure remained lower than the venous pressure. David *et al.* (1935) reported three cases in whom fatal intracerebral hæmorrhage followed the operative relief of longstanding intracranial pressure. The authors explained the hæmorrhages as being due to mechanical factors coupled with hypothetical damage to the hypothalamus. Their argument that the trauma of ventricular puncture was not a causative factor is not convincing. Only one case of extradural hæmatoma following ventricular puncture can be found in the literature (Peet, 1940), but no details concerning it are available.

A common experience of neurosurgical practice illustrates the mechanism which produces extradural hæmorrhage. When a bone flap has been turned and the intracranial pressure lowered the dura follows the collapsing brain and by its elastic shrinkage separates from the edges of the bone defect. The fall in intracranial tension allows dural veins to fill with blood and many bleeding points now make their appearance on a dura which may not have bled previously. Particularly severe bleeding may be encountered from beneath the bone edge if a nearby meningeal vein or venous sinus becomes detached from the bone. Stitches then have to be inserted to pull the dura against the bone and muscle grafts applied to bleeding points.

In conclusion some practical points that emerge from the experience of these three cases may be stated. Intracranial bleeding may result from open ventricular drainage. Young individuals whose ventricles are greatly enlarged are particularly prone to this complication. A deterioration in a patient's state of responsiveness following the reduction of intracranial pressure should raise the suspicion that an extracerebral hæmorrhage has occurred, and the diagnosis should be established by exploration through burr holes. One burr hole on either side should be placed over the frontal pole. Cessation of the flow of cerebrospinal fluid was observed in all three patients when their clinical state had taken a turn for the worse, and in two patients no fluid could be obtained from the opposite ventricle. If present this sign should confirm the suspicion of intracranial hæmorrhage; its absence should not delay exploration. Air may remain for many days following ventriculography in ventricles which have no communication with the subarachnoid space—e.g. in cases of iter stricture. In these patients a rapid and decisive answer to the question whether a clot is present or not might be obtained from an X-ray examination.

Summary

1. Ventricular drainage caused fatal intracranial hæmorrhage in three patients.

2. Young individuals with chronic hydrocephalus appear to be most prone to this complication.

3. Detachment of the dura and venous hyperæmia are offered as explanations of the hæmorrhages.

The author is indebted to Professor Jefferson for his kind permission to publish these cases and for his help in the preparation of the paper.

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LYMPHO-EPITHELIOMA OF THE THYMUS

NERVOUS AND OTHER CLINICAL SYMPTOMS IN THE ADULT

BY

F. PARKES WEBER and K. BLUM

(RECEIVED 8TH SEPTEMBER, 1942)

IN this paper we are concerned, not with the simple tumours—fibroma, lipoma, lymphangioma, lymphosarcoma, round-cell sarcoma—which occasionally (though rarely) arise in the thymus, as in other parts of the body, but with those which arise from the essential epithelioid cells of the thymic medulla associated in greater or lesser proportion with lymphocyte-like cells (probably really lymphocytes), such as constitute the normal thymic cortex. These primary thymic tumours—true "thymomata"—may be termed "lympho-epitheliomata" (Grandhomme, 1900; Schmincke, 1921; Regaud, 1921), and are much less often malignant than are the primary lympho-epitheliomata of the tonsils, pharynx, and naso-pharynx (Cappell, 1934; Harvey, Dawson and Innes, 1937). For recent histological accounts of thymic lympho-epitheliomata, see Wu (1935) and Obiditsch (1937).

The thymic lympho-epitheliomata seem in some cases to exert an endocrine effect, and are specially related to myasthenia gravis. Most important and interesting was the original observation by Weigert (1901) of a thymus tumour in a case of myasthenia gravis in which he wrongly interpreted the "lymphorrhages" in the muscles as tumour-metastases. To these questions we will return in the discussion further on, but for a summary of the literature of the subject we must refer to the recent papers by Gold (1935), Meister (1936), Norris (1936), Miller (1940), Blalock *et al.* (1941), and Poer (1942).

Case Record

The patient, Mrs. F. F., aged 58 years, was admitted on 5th November, 1941, with irregular pyrexia of uncertain origin. The history was that after a sore throat 6 weeks ago she had been suffering from pains in various parts. Blood-count: Hæmoglobin, 60 per cent.; erythrocytss, 3,610,000; colour-index, 0·8; leucocytes, 9,000 (polymorphs, 53 per cent.; lymphocytes, 40 per cent.; monocytes, 7 per cent.). Blood-sedimentation: first hour, 70; two hours, 120. Blood-culture: negative. Urine: nothing abnormal. By auscultation a blowing systolic murmur could be heard in the left intercostal space close to the sternal margin. X-ray examination of the heart (Dr. F. G. Wood) showed a rounded mass projecting to the left of, and apparently continuous with, the heart shadow and moving with it; right and left oblique views were thought to point to this projection being an enlargement of the pulmonary artery and conus (Fig. 1). Brachial blood-pressure: 135/80 mm. Hg. Blood-Wassermann reaction: negative. Ophthalmoscopic examinations (Dr. C. Markus) showed hyperæmia, especially left eye, apparently connected with hypermetropia. The patient at various times complained of a severe kind of acroparæsthesia and of numbness (no real anæsthesia) of the right lower limb and afterwards of the right upper limb and both lower limbs. Severe cramps were sometimes complained of. The knee-jerks, which were equal and natural on admission, were unequal at the end of November, the left one being greatly exaggerated. In March 1942 the patellar and Achilles reflexes were absent on both sides; the triceps reflex was absent on the right side, present on the left side; the planter reflex was of the normal flexor type on both sides; no superficial abdominal reflexes were obtained. Both pupils reacted normally. The speech was rather sluggish. Very little tactile responses in either lower limb; some hypersensitiveness to pressure over the sciatic nerve, both sides. The patient tended to keep her knee-joints flexed. Although general asthenia was very marked, no definite characteristic features of myasthenia gravis were noted.

Focal infection was thought of, but no focus could be discovered. There was moderate fever from admission to 25th November—then a little at the commencement of December and from 10th December to the commencement of January 1942. About 5th February there was again fever, and then from 22nd February to the patient's death on 17th March, 1942, which was due to a final broncho-pneumonia with some decubitus. Frequent profuse night sweatings constituted also a clinical feature. The last blood-culture yielded a growth of staphylococcus albus. Amongst the drugs tried sulphapyridine on one or two occasions seemed to exert temporary beneficial effect.

Necropsy

Over the front upper part of the heart and slightly to the left, firmly connected with the fibrous layers of the parietal pericardium, was a bun-shaped mass, about the size of half a large orange, 14×8×6 cm. in measurement (weight after preparation as a museum specimen: 112 gm.). The multilocular cystic central portion of the mass had a honeycomb appearance on section; most of the cysts freely communicated with each other and were filled with a slimy, translucent mucoid fluid; their walls had a smooth inner surface. In the upper portion of the "tumour" was a slightly larger cavity, which was filled with what macroscopically appeared to be pus, but no microbes could be detected in a film stained with methylene blue, or by Gram's method.

Thyroid gland: slightly enlarged, showing nodular adenomatous condition, one of the nodules in the left lobe having a calcified capsule. Broncho-pneumonia of the lower lobe of the right lung; purulent bronchitis. Nothing specially noteworthy in the other organs: brain, heart, liver, spleen, pancreas, adrenals, kidneys, uterus, ovaries, gastro-intestinal tract, larynx.

Microscopical Examination

The solid part of the mass consisted of a dense collagenous fibrous framework, in which were embedded cellular islands consisting of delicate spindle and epithelioid cells with vesicular nuclei, associated with lymphocyte-like cells as in so-called thymic lympho-epitheliomata (Fig. 2). No Hassal's corpuscles were seen, but at one spot several elongated, slightly curved (" banana-shaped ") vesicular nuclei were noted, grouped together, so as to suggest a faint attempt at the formation of a Hassal's corpuscle. In their shape some of the so-called " spindle cells " resemble rather the cells of " oat-cell " bronchial carcinoma. Microscopical examination of what macroscopically had appeared to be pus showed that it consisted of this cellular material breaking down (" softened ") as a result of (ischæmic?) necrosis. It may be mentioned that a film of this " pseudo-pus " stained with methylene blue showed the presence of a considerable number of tissue mast-cells, which were not clearly differentiated in sections stained in other ways. The honeycomb cystic portion of the tumour represented apparently a further stage of aseptic necrotic involution of the lympho-epitheliomatous tissue. The process was probably analogous to the occasional changes in the thymus gland of children leading to the formation of Dubois's " abscesses " or pseudo-abscesses formerly supposed to be necessarily connected with congenital syphilis.

Is the mass to be regarded as a real lympho-epitheliomatous tumour of an ectopic thymus (or thymic " rest ") with secondary cystic degenerative changes, as above explained, or is it an example of hypertrophy of an ectopic thymus (or thymic " rest ") containing cysts resulting from involutionary focal ischæmic necrotic processes (Kopač, 1939)? The spindle and epithelioid cells resemble those of normal thymic medulla and the lymphocyte-like cells resemble those of normal thymic cortex—which most authors now regard as true lymphocytes —but the grouping of these two constituent types

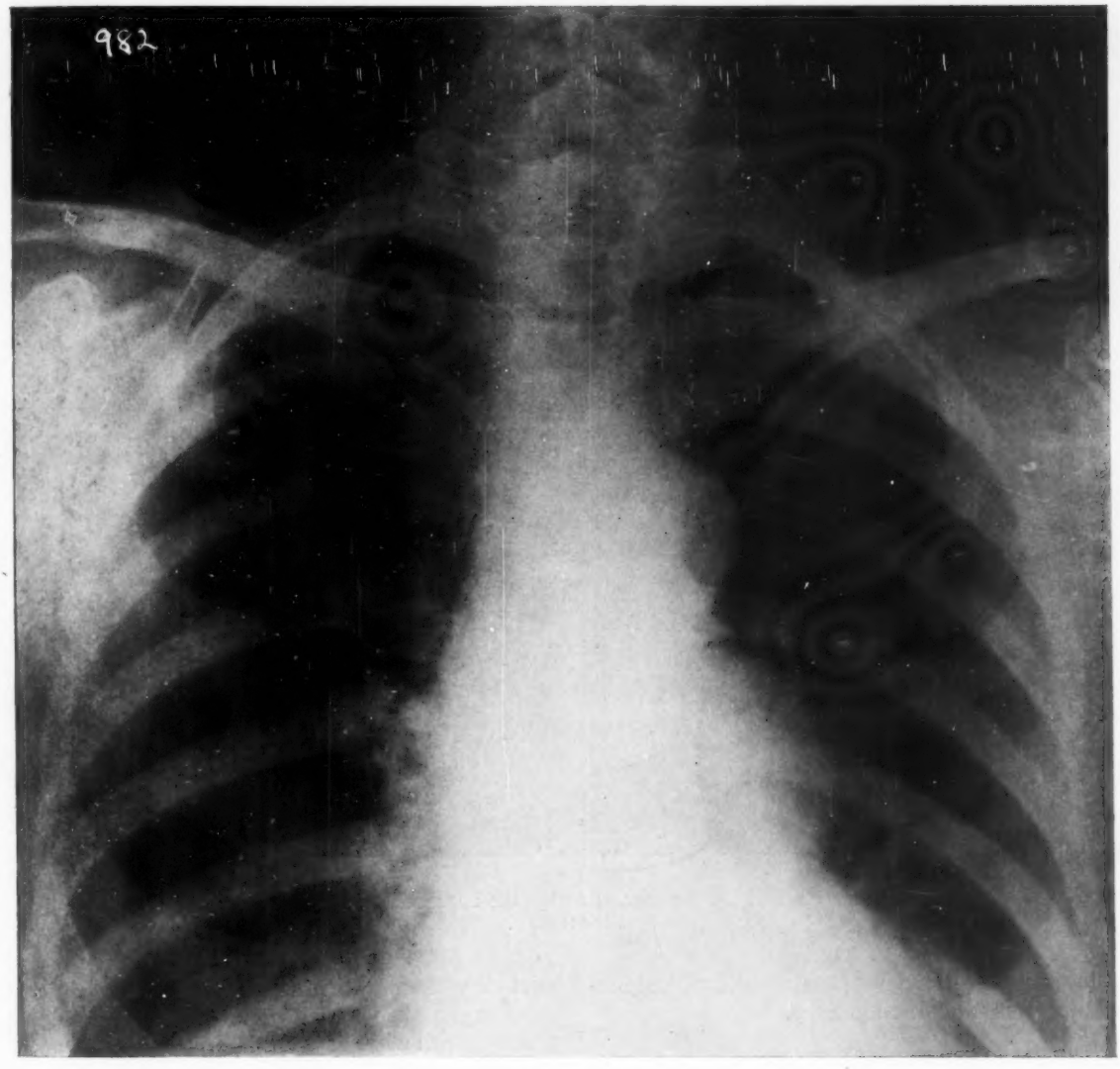

FIG. 1.—Radiogram of the thorax taken on 20th November, 1941.

of cells is not sufficiently clearly marked out into cortex and medulla to permit the mass to be regarded as the result of mere thymic hypertrophy; nor does the complete absence of Hassal's corpuscles favour the view of mere hypertrophy. The mass must therefore, we think, be regarded as a true primary thymic lympho-epitheliomatous tumour (" thymoma "). Whether the tumour is a primary one of an ectopic thymus or of a thymic " rest " makes no difference from the pathological point of view; we did not specially search for any thymic remnant in the normal position. By our term " ectopic " we do not imply that the position of the tumour, in front of the pericardium, is abnormal for thymic tissue in early childhood. In the present case there were no cells functionally still resemble the cells of simple hyperplasia.

In something like 55 per cent. of cases of myasthenia gravis hypertrophy or primary tumour (lympho-epithelioma) of the thymus has been present, but in reality the percentage is probably considerably higher, for in many cases thymus or thymic tumour has not been sufficiently looked for. On the other hand, myasthenic symptoms may have been overlooked in some cases of thymic tumour in surgical wards (Mann, 1934). Although in our present case characteristic symptoms of myasthenia gravis were absent, it is highly probable that the great general asthenia, the extreme acroparæsthesia, numbness and other nervous symptoms were in some way con-

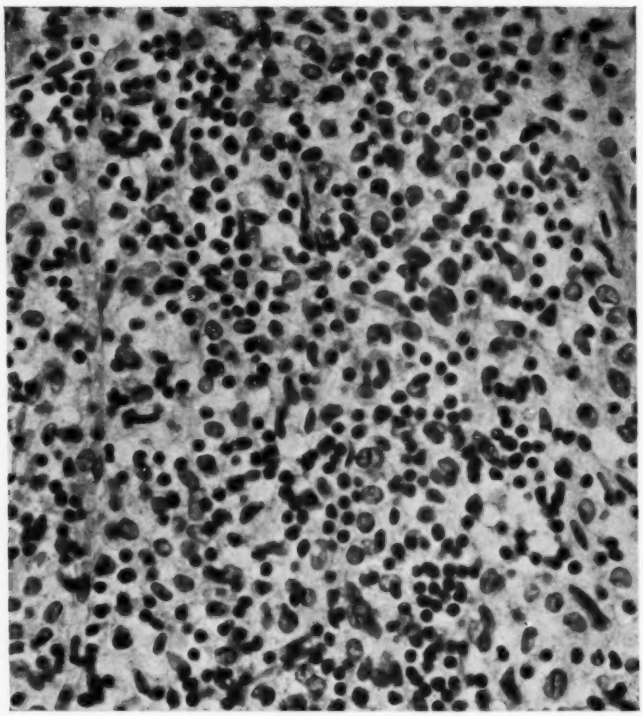

FIG. 2.—Photomicrograph of part of the tumour, showing the characteristic epithelioid and lymphocyte-like cells (×400).

metastases and nothing in the microscopical examination pointed to malignancy.

Discussion

Clinical symptoms from thymic hypertrophy or tumour may of course be mechanical, from local pressure, and in the present case the systolic murmur heard to the left of the sternum was probably due to tumour pressure.

If the thymus is an endocrine organ one would expect that constitutional endocrine symptoms would often result—as they often do in primary tumours of other endocrine organs—from a primary neoplasm arising from the essential (endocrine) cells, that is to say, so long as the neoplastic cells still retain something of the original functional (endocrine) activity, in fact, so long as the neoplastic nected with the thymic tumour. The recurrent sweating and pyrexial periods may possibly, by analogy with what happens in some cases of lymphogranulatosis maligna, be atrributed to the necrotic softening and formation of " pseudo-pus " in the lympho-epithelioma, with resulting toxic absorption. Patients with thymic lympho-epithelioma, according to the literature (Matras and Priesel, 1928; Zajewloschin, 1929 and 1933; Nemenow, 1932; Ercklentz, 1936), have died of pleuritis, empyema, pneumonia, furunculosis, and decubitus. The loss of resistance to toxic-infectious agents culminated in our case with the decubitus and broncho-pneumonia, the latter first manifest 4 days before the patient's death, the former a week earlier. It is possible that the absence of definite symptoms of myasthenia gravis might be due to the diminution of the (pre-

sumable active) function of the epithelioid cells consequent on the necrotic softening of many of the latter associated with the formation of the "pseudo-pus" and cysts.

In regard to clinical diagnosis the X-ray shadow of a thymic tumour is of great importance. In our case it seemed to move with the pulsation of the great vessels and to be continuous with the heart shadow. The position of the tumour in the anterior mediastinum overlapping the parietal pericardium on the left was not made out during life. In the differential diagnosis during life cardiac aneurysm, pericardial tumour, mediastinal lymphogranuloma, mediastinal gumma, mediastinal phlegmon, and congenital dilatation of the pulmonary artery might be thought of. Had the correct diagnosis been made at an early stage, our case would have been an ideal one, if not for surgical excision of the tumour, at least for treatment by X-rays or radium.

The possible part played by the thymus gland in some cases of Graves's Disease is suggested by the occasional occurrence of myasthenic symptoms in the latter disease and even by satisfactory results of thymectomy (Schumacher and Roth, 1913; Russell Brain, 1938; Adler, 1939). Fraser (1937) recorded the case of a woman suffering from myasthenia gravis and Graves's Disease, who temporarily completely lost her myasthenic ophthalmoplagic symptoms under the influence of prostigmin. Dudgeon and Urquhart (1926) in nine cases of Graves's Disease found muscle "lymphorrhages" similar to those of myasthenia gravis.

It seems that in very rare cases malignant thymoma or primary carcinoma of the thymus may by some unknown process disturb the endocrine balance in such a way as to give rise to symptoms somewhat resembling Cushing's syndrome (Leyton, Turnbull and Bratton, 1931), but into this question of the "Leyton-Turnbull-Bratton syndrome" we cannot enter here.

For help in the microscopical examination we have specially to thank Dr. J. R. Gilmour, Dr. R. W. Scarff, Dr. H. M. Turnbull, Dr. J. G. Greenfield, and Dr. A. H. T. Robb-Smith. We owe the photomicrograph to Dr. Greenfield. The tumour itself is now in the Museum of the Royal College of Surgeons.

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Innervation and "Tonus" of Striated Muscle in Man.—In a study of normal subjects and of patients suffering from various diseases of the nervous system, Hoefer attempts to determine by analysis of action potentials to what extent the clinical concept of normal and abnormal tone of skeletal muscle is covered by that of postural myotatic reflex regulation. In cases of spasticity no impulses are to be recorded from the muscles at rest. Spasticity is an exaggeration of the normal stretch reflex. The response may be produced by proprioceptive as well as by heteroceptive stimuli. Rigidity differs from spasticity in that a basic continuous influx of impulses is found at rest, while, in addition, the stretch reflex is exaggerated in a manner very similar to that associated with spasticity. In rigidity a component of "tonic" activity is found which is not understandable in terms of postural segmental regulation. (R. M. S.)

Diagnosis and Management of Subarachnoid Hæmorrhage.—In a study of subarachnoid hæmorrhage a series of 120 hospital-treated patients are presented, the youngest of whom was 3 weeks and the oldest 75 years of age. Fifty-five were females and 65 males. The condition of 27 was of unknown origin; in 30 it was due to arteriosclerotic degeneration of the vessel walls, in 9 to trauma, in 25 to ruptured intracranial aneurysm, and in 16 to the action of bacteria or their toxins on small capillaries; in two it was secondary to massive cerebral hæmorrhages, in 3 it followed intraventricular hæmorrhages, in 4 it was caused by a blood dyscrasia, and in 4 it accompanied a vascular cerebral neoplasm. Of these 120 patients, 41 died and 79 recovered. (R. M. S.)

Sympathetic Nervous System.—Evidence is presented to show that a sympathectomy has a pronounced influence on the interpretation of high and low temperatures when the sympathectomized part is compared simultaneously with a normally innervated part. A cold object feels warmer and a hot object feels cooler to the sympathectomized hand than to its normal mate. When a sympathectomized zone of the skin is tested alone no alteration can be elicited in the sensibility to or the discrimination of touch, pain, and temperature as compared with these faculties on the normal side. A sympathectomy diminishes, and almost abolishes, the aching and stinging pain in the hand and foot that results from exposure to severe cold. (R. M. S.)

Amyotrophic Lateral Sclerosis.—Forty-two cases of amyotrophic lateral sclerosis were studied histopathologically with reference to the origin and extent of the lesion of the upper motor neuron. Disease of the upper motor neuron originated in the giant pyramidal cells of Betz in only about one-third of the cases, while in the remaining two-thirds the pyramidal tracts became involved in the pons, the medulla oblongata or the spinal cord. The duration of the illness had no influence on the extent of involvement of the giant pyramidal cells of Betz. The causative agent of amyotrophic lateral sclerosis has a predilection for attaching the upper neuron either at its point of origin (the motor cortex) or anywhere along its course, but chiefly in the brain stem and the spinal cord. As further proof that the pyramidal pathways become involved anywhere along their course is the concomitant implication of other ventrolateral tracts of the spinal cord, for example, the spinothalamic and the spinocerebellar, in 21, or one-half, of the cases. From the point of view of the lesion of the upper motor neuron, amyotrophic lateral sclerosis can be classified anatomically into forms originating in the cortex, the peduncle, the brain stem, and the spinal cord. Pathologically, 36 cases belong to the degenerative and six to the inflammatory type. (R. M. S.)

Ruptured Aneurysm of Left Anterior Cerebral Artery.—A case of moderately large ruptured saccular "berry" aneurysm of the left anterior cerebral artery occurring in a man of 54 is reported. The disturbed vascular supply resulted in swelling of the left frontal lobe, causing dislocation and herniation of the brain stem through the incisura with resultant notching of the contralateral crust by the free edge of the tentorium, thereby producing ipsilateral cerebral signs. Attention is called to the disturbed state of consciousness and the behaviour of the patient both with regard to the problem of differential diagnosis and the explanation to be found in the pathological state of the cortex and subcortex of the left frontal lobe. (R. M. S.)

Vitamin E Therapy of Neuromuscular Disorders.—The author was unable to demonstrate any outstanding clinical response to the use of vitamin E and alpha tocopherol in the treatment of amyotrophic lateral sclerosis and progressive spinal muscular atrophy with progressive bulbar palsy. (R. M. S.)

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Vascular Pattern of Lesions of Multiple Sclerosis.—Two-thirds of the lesions in multiple sclerosis were orientated about the veins. This seems to indicate that, whatever proves to be the causative agent, either the tissues about the veins are more susceptible to it or it is concentrated in its effect at this site. As regards pathological changes in the veins themselves, it is suggested that the thrombi observed are the result of the local absorption of thromboplastic substances released by the rapid breakdown of myelin sheaths. (R. M. S.)

Hemangioma of Vertebra with Compression of Cord.—

A case is reported in which roentgen therapy was employed as the sole means of treatment and in which an excellent result was obtained. (R. M. S.)

Age and Convulsions.—Experiments on rats show that the ability of acid fuchsin to enter the central nervous system decreases with age and that its ability to produce convulsions varies accordingly. (R. M. S.)

Biochemical Disturbances in Mental Disorders.—By means of the biochemical test they describe, the authors claim to be able to differentiate at least two forms of schizophrenia. In about 60 per cent. of the cases, the schizophrenic pattern is characterized by the presence of an anti-insulin factor; in the remaining 40 per cent. in whom the anti-insul factor is absent, the clinical pattern or syndrome may be due to other disturbances. (R. M. S.)

Continuous Ambulatory Insulin Shock Technique.—The authors recommend that patients with chronic schizophrenia of long standing should be treated daily with mild hypoglycæmic shocks for an indefinite period. (R. M. S.)

Cerebral Fat Embolism.—In fat embolism the changes within the central nervous system result from the plugging of the blood vessels by fat emboli. Within the gray matter anæmic infarcts are the usual lesions, while within the white matter hæmorrhagic infarcts are more common. Unless death follows quickly the lesions are of different ages. They explain the progressive cerebral picture. (R. M. S.)

Vasospasm and Focal Cerebral Ischemia.—The effects of mechanical and electrical stimulation on the pial vessels of thirty cats, one dog, and four monkeys have been studied. The pial vessels in cats contract vigorously on mechanical or electrical stimulation. The dog's pial vessels are not as sensitive to this type of stimulation as the cat's; the monkey's are less so than the dog's. Such evidence as there is suggests that these spasms are not dependent on a neurovascular mechanism. They re-emble closely the local spasms in peripheral vessels described by Lewis and others as muscular, and not neuromuscular. They are localized to the site of stimulation and are not propagated, as are the neurovascular reactions described by Ricker and Chase in the mesenteric vessels of rabbits. (R. M. S.)

Avian Thiamine Deficiency.—Using dietary methods described before and staining methods which demonstrate the neurofibrillar structure of the neuron, the following observations were confirmed: (1) the first neuronal histological change in thiamine-deficient pigeons is degeneration of the distal part of the axon, and changes in myelin are secondary to this; (2) degeneration proceeds centralward and is accompanied by slight shrinkage or sclerosis of the cell body; (3) the large nerve fibres degenerate first and the medium later, the small fibres usually remaining intact; and (4) opisthotonos may not be attended by any definite neurological lesions. In the present study the early axonal changes were shown to consist of thickening of the neurofibrils and generalized swelling, followed by the formation of varicosities, in the distal parts of cell processes. This is followed by fragmentation. The following generalization may be made: The neurological manifestations of an acute or a chronic deficiency in thiamine are accompanied first by impaired function and then by degeneration of the primary neurons of the proprioceptive nervous system and the central terminations of the optic nerves. Changes occur next in internuncial neurons of these same systems. Finally, after prolongation of the deficiency, the efferent nervous system becomes affected. (R. M. S.)

Amyloid Neuritis.—In a case of non-septic amyloidosis extensive degeneration was found in the peripheral nerves. These were of ischæmic origin, the blood vessels having undergone narrowing or occlusion from the presence of amyloid in the media. (R. M. S.)

Section of Vagus-Spinal Accessory Complex.—Operative section of the cephalic third of the vagus-spinal accessory complex was followed by sensory changes over the larynx and lower portion of the pharynx; no evidence of disturbance of motor function, other than transient rise in pulse rate and blood pressure, occurred. After section of the cephalic third of the vagus-spinal accessory complex, motor fibres central to the section remained intact while sensory fibres showed evidence of degeneration up to the nucleus of the tractus solitarius. It was thus possible to differentiate clearly sensory from motor fibres in the cut roots. Most of the sensory fibres of the vagus nerve are contained within the cephalic third, approximately, of the vagus-spinal accessory complex. These sensory fibres occur within the large dorsal roots, which also contain a few motor fibres. (R. M. S.)

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Neuroanatomic Complications of Spina Bifida.—In many instances of spina bifida (spinal dysraphism) there is abnormal fixation of the spinal cord which precludes its adequate rostral migration with continued development. This abnormal fixation in some cases results in a pleomorphic variety of neuroanatomical alterations in distant parts of the nervous system. These alterations are: (1) Short cauda equina and low-lying conus medullaris. (2) Abnormal stretching of the spinal cord above the site of fixation. (3) Elongation of the hindbrain, with localization in the vertebral canal of the medulla oblongata, the choroid plexus of the fourth ventricle and parts of the cerebellum. (4) Dysplasia of some of the cerebellar folia. (5) Elongation of the lowermost cranial nerves with their compression at the foramen magnum by the impaction of the hindbrain. (6) Stenosis of the aqueduct of Sylvius. (7) Internal hydrocephalus due to stenosis of the aqueduct of Sylvius and to impaction of the hindbrain in the foramen magnum. (8) Deformity of the medulla oblongata and of the hind end of the fourth ventricle. (9) Hydromyelia of the uppermost cervical levels of the spinal cord. (10) Syringomyelic-like cavitation in the cervical portion of the spinal cord. (11) Pressure on the anterior spinal arteries and the vertebral system of veins at the foramen magnum. (R. M. S.)

Pyruvic Acid in Wernicke Syndrome.—Patients with the Wernicke syndrome show inability to metabolize pyruvic acid properly. After prolonged treatment with thiamine hydrochloride and with thiamine hydrochloride plus other members of the vitamin B complex, this defect in pyruvic acid metabolism is corrected. This is

associated with disappearance of the ophthalmoplegia and improvement in the mental status. The authors' clinical and chemical observations, together with the pathological changes previously reported by Alexander and his co-workers, demonstrate that the Wernicke syndrome is invariably associated with a deficiency of thiamine. (R. M. S.)

Metrazol Convulsions under Nitrous Oxide Anæsthesia.—Three hundred and twenty-three metrazol injections were made into 40 patients under nitrous oxide anæsthesia. This method was found to avoid the fear reaction so common in metrazol shock therapy without altering the convulsive pattern or the duration of the convulsion. Little or no increase in the dose of metrazol was necessary to produce convulsions when the patient was under anæsthesia. Traumatic complications were minimized with this method (5 per cent.), and it is suggested that anæsthetizing the patient may be an aid to their avoidance. Therapeutic results in cases of melancholia and schizophrenia were comparable to those obtained by orthodox metrazol therapy. The method adds further direct proof for the contention that fear plays no role in metrazol convulsive therapy. The technique is offered as a simple means of improving rapport and diminishing resistiveness in patients undergoing this therapy. (R. M. S.)

Emotional Excitement and Insulin Content of Blood.—The results of investigations reported in this paper show clearly that the insulin content of the blood of normal and that of psychotic subjects are the same. Apparently, psychotic and normal persons do not differ with regard to the secretion of insulin in periods of rest but differ only with respect to the reactivity of the autonomic centres controlling the secretion of insulin via the vagus nerve and the recreation of epinephrine via the sympathetic system. (R. M. S.)

Convulsive Seizures and Rheumatic Heart Disease.—The incidence of convulsive seizures in patients with rheumatic heart disease is higher than the incidence in the general population. (R. M. S.)

Patterns of Breathing and Personality.—A type of breathing characterized by a smaller volume of tidal air and greater regularity is found among chronic " schizophrenic " patients more commonly than among normat persons. The mode of breathing is an index to some of the personality components of normal persons. Those sharing to a greater degree the breathing characteristics common among schizophrenic patients are found frequently to be " schizoid " in disposition. Suggestive evidence is presented for the existence of racial characteristics in the breathing pattern. These have been demonstrated in races whose personality configurations are also generally distinctive. (R. M. S.)

Intraspinal Meningiomas.—Meningioma is the product of an admixture of elements—the specialized arachnoid-type cell, its multipotential stroma and at times dural components as well. The tumour is of neural crest origin, and its only mesoblastic structures are a result of dural attachment. One hundred and thirty intraspinal meningiomas have been classified into eight types. Each tumour has been examined both clinically and pathologically. Diffuse meningomatosis, the heoplastic transformation of embryonically arrested leptomeninges, has been delineated in a separate category and differentiated from gliomatosis, sarcomatosis and melanomatosis of the meninges. (R. M. S.)

Section of Spinothalamic Tract at Level of Inferior Olive.—Evidence is presented indicating the efficacy of section of the spinothalamic tract in the medulla for relief of high, intractable pain. The results of the operation in a case of carcinoma of the breast with metastases are given. By means of the Marchi technique, the courses of the spinothalamic, spinotectal and ventral spinocerebellar tracts have been followed through the brain stem. The position of the spinothalamic tract in relation to the inferior olive has been ascertained, and a topical arrangement of fibres within the tract is described. Fibres from the lower dermatomes occupy a lateral position, while fibres from the upper ones lie medially. (R. M. S.)

Estrogen Therapy of Depressions with Menopause.—Diethylstilbestrol has been sufficiently effective in the trials reported here to warrant further use in the treatment of involutional melancholia. (R. M. S.)

Danlos-Ehlers Syndrome.—In the case here described the diagnosis of Danlos-Ehlers syndrome can be made. There were hyperelasticity of the skin, hypermotility of the joints and a tendency to form abnormal and deficient scar. Multiple small tumours of the skin, however, were not found. During the course of hospitalization for bladder diverticulectomy, transient paralysis of the left vocal cord developed. A review of the history disclosed that on previous occasions similar short-lived episodes of difficulty in speaking had occurred. The cause of the paralysis of the vocal cord is not known; the relation between it and the Danlos-Ehlers syndrome is discussed. (R. M. S.)

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*Encephalitis with Intranuclear Inclusion Bodies: A Clinicopathologic Study. A. J. Akelaitis and L. J. Zeldis. 353.
*Variations of Electroencephalogram Associated with Electric Shock Therapy of Patients with Mental Disorders. B. L. Pacella, S. E. Barrera, and L. Kalinowsky. 367.
*Changes in the Brain after Electrically Induced Convulsions in Cats. B. J. Alpers and J. Hughes. 385.
Experimental Pharmacology of Postencephalitic Parkinson's Disease. J. Loman, P. G. Myerson, and A. Myerson. 399.
*Multiple Sclerosis in the American Negro. L. C. Kolb. 413.
*The Human Pyramidal Tract: V. Postnatal Changes in the Axons of the Pyramids. A. M. Lasser. 422.
Otitic Thrombosis of the Cerebral Sinuses and Veins Simulating Multiple Brain Tumor. M. Keschner and C. Davison. 428.
*The Graphic Rorschach Test I. G. N. Rocklin and K. N. Levine. 438.
*Electroencephalographic Effects of Acute Increases of Intracranial Pressure. F. M. Forster and L. F. Nims. 449.
*Two Minute Clinical Test for Measurement of Intellectual Impairment in Psychiatric Disorders. M. Hayman. 454.
Case Reports:
*Primary Degeneration of the Corpus Callosum (Marchiafava's Disease): Report of the Second American Case. M. G. Bohrod. 465.
Spina Bifida with Meningocele: Occurrence in Two Children of the Same Family. B. H. Shulman. 474.

Encephalitis with Intranuclear Inclusion Bodies.—A clinicopathological study of a necrotic form of encephalitis with type A intranuclear inclusion bodies is reported. The topographical distribution of the lesions is unlike that found in those diseases of the nervous system which are commonly regarded as being of a virus nature. From a review of the literature it is probable that this is a form of encephalitis described originally by Dawson. (R. M. S.)

Variations in Electroencephalogram.—Patients subjected to the generalized convulsive seizure or to a series of generalized convulsions exhibited fairly marked changes in their electroencephalographical patterns, resembling in type those observed after convulsions produced by other means or occurring spontaneously. The larger the series of treatments administered, the more pronounced became the abnormalities and the greater the duration of time for which these abnormalities persisted. In general, the electroencephalographical abnormalities associated with electric shock treatments are for the most part " reversible " in the sense that they gradually disappear. It should be stressed that this does not necessarily imply that any concomitant functional or histopathological disturbances which may occur as a result of the treatments are also correspondingly " reversible." (R. M. S.)

Changes in Brain after Electrical Convulsions.—Electrically induced convulsions were produced in 30 cats. Subarachnoid hæmorrhage, usually of mild

degree but sometimes extensive, was found in 14 cats. Hæmorrhage in the brain substance (cerebral cortex and white matter, cerebellum, region of the third ventricle and third ventricle) was found in 9 cats, usually of a punctate type but more extensive in two instances. Whether similar changes are to be expected in human beings treated with electric shock cannot be determined from this material. (R. M. S.)

Multiple Sclerosis in American Negro.—Negroes in Baltimore are as subject to multiple sclerosis as the native and the foreign-born white population. The clinical features of the disease in the Negro are similar to those seen in the white man. The disease in the Negro is often mistaken for syphilis and in some instances may occur with syphilis in the same person. (R. M. S.)

Human Pyramidal Tract.—The fibres of the pyramidal tract undergo the following postnatal changes. Early in life all the axons are apparently present and are small, delicate, uniform in calibre, crowded and possibly of different chemical nature than when mature. During this period they may be nonfunctional and vulnerable to small lesions. At 8 months of age, when voluntary movements are attempted, certain fibres commence to expand at a more rapid rate than others. Individual growth continues, until at 2 years of age the pyramidal tract simulates in miniature that of an adult. At 22 years of age the pathway possesses a few large, more medium, and many minute axons. In senility, on the basis of observations on one specimen, there is a decrease in number and diameter of fibres. It seems reasonable, also, to conclude from the study that integration of the pyramidal tract occurs through morphological and chemical changes in both the axons and the myelin sheaths rather than in the latter alone, and that different physiological motor states may be explainable, in part at least, on a neuroanatomical basis. (R. M. S.)

Graphic Rorschach Test 1.—An original graphic technique and procedure is described which is designed to act as a confirmation, supplement, and extension of the Rorschach method. (R. M. S.)

Electroencephalographic Effects of Increased Intracranial Pressure.—Animal experiments show that the electroencephalogram is altered by acute rises of intracranial pressure only when the increases are sufficient to alter cerebral blood flow. The pressures required for these acute effects lie for the most part beyond those of clinical experience. Cushing's phenomenon (rise in blood pressure in response to increased intracranial pressure) occurs in the absence of electrical activity of the cortex. (R. M. S.)

Measurement of Intellectual Impairment in Psychiatric Disorders.—A simple two-minute clinical test for the measurement of mental impairment is described. The test, consisting of the serial subtraction of 7 from 100, was standardized for mental age on a group of 433 normal persons. Nine hundred responses from 580 patients with a wide variety of psychiatrical disorders were analysed. Its advantages as a quickly applicable and reasonably accurate test for intellectual efficiency are emphasized. (R. M. S.)

Primary Degeneration of Corpus Callosum.—This report on primary degeneration of the corpus callosum (Marchiafava's disease), records the forty-third case in the medical literature and the second in the United States, all the other cases having been reported from Italy. The patient was of Swiss ancestry and, like the great majority of similarly affected persons, was a chronic alcohol addict.

The essential pathological process was one of demyelination with reactive proliferation of phagocytic glia cells and blood vessels.

It is suggested that, in common with Wernicke's hæmorrhagic encephalitis and other degenerations of the nervous system associated with alcoholism and other toxic agents, the essential etiological moment is a deficiency of a member of the vitamin B complex, probably of that constituent known as vitamin B_1 or thiamine.

In common with other degenerative processes, a constitutional factor is of marked importance. The racial factor so consistent in this disease may determine the site of degeneration in the corpus callosum. (R. M. S.)

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*Studies on the Corpus Callosum: 1. Laterality in Behaviour and Bilateral Motor Organization in Man before and after Section of the Corpus Callosum. K. U. Smith and A. J. Akelaitis. 519.
*Tractotomy for Relief of Trigeminal Neuralgia. H. Olivecrona. 544.
*Western Variety of Equine Encephalitis in Man: A Clinicopathologic Study. A. B. Baker and H. H. Noran. 565.
*The Amnestic Syndrome. T. Lidz. 588.
*Factors affecting Changes produced in Electroencephalogram by Standardized Hyperventilation. H. Davis and W. McL. Wallace. 606.
*Vascular and Interstitial Cell Changes in Thiamine-Deficient Animals. M. Prados and R. L. Swank. 626.
*Myasthenia Gravis Treated by Excision of Thymic Tumor: Report of Two Cases. E. Campbell, N. F. Fradkin, and B. Lipetz. 645.

Case Reports:
Suprasellar Aneurysm: Report of a Case, with Recovery. R. M. Klemme and R. D. Woolsey. 662.
*Hemichorea (Hemiballismus): Association with a Pallidal Lesion, Involving Afferent and Efferent Connections of the Subthalamic Nucleus; Curare Therapy. J. W. Papez, A. E. Bennett, and P. T. Cash. 667.

Studies on Corpus Callosum.—The present study tends to deny the view that sidedness is unitary in character, as well as the view that the central balances related to different aspects of sidedness are neurologically a unitary system. The complex character of sidedness has been brought out especially clearly in relation to eye dominance and other aspects of sidedness. The profile method of measuring sidedness devised in this study shows, in addition, that many different types of motor performance display varying degrees of sidedness and are not uniformly affected by lesions of the nervous system. In general, the results of this study and additional consideration suggest that any uniformity in sidedness in the subject is probably derived from strong original imbalances in the neural mechanisms of the postural system early in life and the integration through learning of correlated lateral habits with this primary neural sidedness. (R. M. S.)

Tractotomy and Trigeminal Neuralgia.—Section of the spinal trigeminal tract may be regarded as an attempt to cure the neuralgia without having to pay the price of complete anæsthesia in a large part of the trigeminal area. In those cases in which the neuralgia is of extreme severity and the age and general condition of the patient are such as to make a secondary operation within the next few years a serious possibility tractotomy is contraindicated. Tractotomy therefore is best suited for comparatively young persons with neuralgia of moderate severity. In cases of bilateral neuralgia the indication for tractotomy is more urgent than in the ordinary case of unilateral pain because of the disability attending complete anæsthesia of both sides of the face. Bilateral section of the spinal trigeminal tract can be done safely in one stage provided the operator satisfies himself after the procedure on the first side is finished that no posticus palsy has occurred. (R. M. S.)

Equine Encephalitis in Man.—Ten cases of Western equine encephalitis occurring in man are reported. In 5 cases the termination was fatal and complete autopsy studies were obtained. The clinical features of this disease are surprisingly consistent from case to case. The onset of the illness is sudden, with generalized headaches, nausea, elevation of temperature and lethargy. After a week or two the symptoms subside. In about 10 per cent. of cases the disease terminates fatally. Neurological signs consist of stiffness of the neck, muscular weakness and hyporeflexis. The spinal fluid shows moderate pleocytosis, with mononuclear cells predominant. In fatal cases, lesions are found scattered

throughout the nervous system, being most noticeable in the region of the basal nuclei. The histopathological changes are characterized by the suppurative nature of the inflammatory elements. Polymorphonuclears are common and form focal, diffuse, and perivascular infiltrations. Mononuclear cells may also be prominent. Petechiae and scattered areas of demyelination are also present and in some cases overshadow the inflammatory lesions. (R. M. S.)

Amnestic Syndrome.—In the amnestic or Korsakoff syndrome, the major manifestations—possivity, confabulation, disorientation, loss of "time sense" and difficulties in altering the orientative set (Einstellungsstörung)—appear as consequences of the disruption of integrated behaviour when the past is not freely available. The hypothesis is offered that both retrogressive deficits and inability to deal with transient events can be understood as parts of the difficulty in freely evoking past experiences. Utilization of post-traumatic events is most seriously disturbed because they are not met by the background of past experience essential to full perception. (R. M. S.)

Changes in E. E. G. by Standardized Hyperventilation.—It is suggested that the appearance of five cycle and delta waves during hyperventilation is due to cerebral vasoconstriction, which in turn causes diminution in the supply of oxygen and dextrose to the cerebral cortex. (R. M. S.)

Vascular Cell Changes in Thiamine-Deficient Animals.—Hæmorrhages occur in the brains of thiamine-deficient pigeons and are accompanied by perivascular sclerosis and interstitial cell proliferation. The hæmorrhages are preceded by vasodilatation and are first perivascular and later infiltrating. In all instances the vascular lesions were preceded or accompanied by degenerative changes in neighbouring neurons and are thought to be due to metabolic changes in the neurons consequent to thiamine deficiency. In very acutely deficient kittens acute swelling of oligodendrocytes and clasmatodendrosis of astrocytes were observed, whereas in chronically deficient kittens the oligodendrocytes were slightly, if at all, changed, and the astrocytes were markedly hyperplastic and hypertrophied. (R. M. S.)

Myasthenia Gravis and Excision of Thymic Tumour.—The literature containing reports of cases in which myasthenia gravis was treated by thymectomy is reviewed. Two additional cases are recorded. One patient is considerably improved, although mild myasthenic symptoms persist after two years; the death of the other, two days after operation, was partially attributable to bronchopneumonia and atelectasis. Further evidence is presented that benign tumour and hyperplasia of the adult thymus are in some way associated with myasthenia gravis. The results of the studies thus far are insufficient to establish whether this relation is primary or secondary. (R. M. S.)

Hemichorea.—A case of hemichorea of the left side is reported in which curare principle was used to control the spontaneous choreiform and ballistic movements. Three perivascular lesions were observed, one in the right pallidum, one in the left prerubral field and one in the right lower optic radiation. The second lesion was in the left prerubral field, directly in the course of the crossed subthalamicotegmental fibres. The subthalamic decussation and a part of the fibres in the right subthalamic nucleus were demyelinated. On the left side a part of the crossed subthalamicotegmental fibres were degenerated below the level of the lesion, as indicated by gliosis. The first lesion was in the frontal end of the right lateral segment of the pallidum and extended across the internal capsule. It destroyed the medial group of the pallidosubthalamic fibres. It also involved a part of the frontopontile fibres, frontal radiation, and strionigral fibres. The subthalamic nuclei were intact, except for loss of myelinated neuropil, gliosis, and some loss of cells in the nucleus on the right side. The third lesion was in the posterior part of the internal capsule and affected a part of the lower optic radiation and adjacent radiations of the pulvinar. The probable explanation of the hemichorea is the degeneration of the pallidosubthalamic and crossed subthalamicotegmental fibres. The possible routes of the released flow of impulses causing hemichorea are discussed. (R. M. S.)

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*The Olfactory-Parotid Reflex: Study of One Hundred and Fifty Patients with Disorders of the Central Nervous System; A Preliminary Report. C. A. Elsberg, H. Spotnitz, and E. I. Strongin. 707.
*Electroencephalographic Studies on Neurosyphilis. K. H. Finley, A. S. Rose, and H. C. Solomon. 718.
*Mixed Tumors of the Spinal Canal. L. A. French and W. T. Peyton. 737.
*The Brain in Sickle Cell Anemia. F. Wertham, N. Mitchell, and A. Angrist. 752.
*Diverticula of the Lateral Ventricles Extending into the Cerebellar Fossa. A. E. Childe and F. L. McNaughton. 768.
Leukocytosis During Various Emotional States. A. T. Milhorat, S. M. Small, and O. Diethelm. 779.
*Intracranial Blood Flow in Dementia Paralytica, Cerebral Atrophy and Schizophrenia. M. Rosenbaum, E. Roseman, C. D. Aring and E. B. Ferris. 793.
*Factor of Hypoxia in the Shock Therapies of Schizophrenia. H. E. Himwich and J. H. Siris. 800.
*Parapyramidal Fasciculotomy in the Brain Stem. J. H. Siris. 808.
*Studies of the Sensation of Vibration: II. Vibration Sensibility in the Face Following Retrogasserian Neurectomy. M. Brown and G. K. Yacorzynski. 813.
*Electroencephalograms of Thiamine-Deficient Pigeons. R. L. Swank and H. H. Jasper. 821.
*Periarteritis Nodosa: A Clinicopathologic Report, with Special Reference to the Central Nervous System. N. Malamud and D. B. Foster. 828.

Special Article:
Some Problems of Wartime Neurology. W. Penfield. 839.

Olfactory-Parotid Reflex.—The resting rate of secretion of the parotid gland was found to be abnormal in 56 per cent. of a series of 64 patients with neurological disorders. Stream injection of the odorous substance, citral, into the nasal cavity produced a definite increase in the volume of secretion from the ipsilateral parotid gland in normal human beings. The effect on the contralateral parotid gland was less marked. It is suggested that the reflex response of the parotid glands on stimulation of the nasal mucosa with odorous substances be called the olfactory-parotid reflex. There is evidence to support the view that the afferent pathway of the reflex is not in the first cranial nerve but involves the fifth and seventh cranial nerves. Neurological disorders produce overactivity and underactivity of the reflex. There is some evidence that the cerebral pathways which affect the reflex cross in their course from the cerebral cortex to the brain stem. (R. M. S.)

E. E. G. Studies on Neurosyphilis.—The electroencephalogram has no significant diagnostic value in neurosyphilis. (R. M. S.)

Mixed Tumours of Spinal Canal.—Three proved cases of mixed tumour of the spinal canal are presented. Characteristic symptoms of mixed tumours are: (a) the long duration of symptoms before the patient becomes incapacitated; (b) the roentgenological evidences of fusiform enlargement of the spinal canal with associated spina bifida. The interpedicular distances of the lower thoracic and lumbar vertebræ in children were measured, and the normal range was found to be less than that of adults. In order to determine whether a spinal canal is enlarged, its measurements must be compared with the normal range in the subject's age group. A spinal canal that is larger than those within the normal range of the interpedicular distance of which increases 2 to 4 mm. in consecutive vertebræ shows evidence consistent with a diagnosis of mixed tumour. (R. M. S.)

Sickle Cell Anæmia.—The essential neuropathological features of sickle cell anæmia are small, necrotic and necrobiotic lesions on a vascular basis, diffusely distributed with predilection for the border between the cortex and the subcortical white matter; marked general hyperæmia and congestion of blood vessels; hypertrophy

and proliferation of endothelial and adventitial elements of the walls of small blood vessels; siderotic pigment in intra-adventitial spaces and adventitial cells; larger vascular lesions of uncharacteristic type (softenings, thromboses, etc.), small hæmorrhages and extravasations; intravascular lipoid material and fat embolism of capillaries and precapillaries; focal and diffuse changes in the nerve cells in cortical and subcortical gray structures, and focal areas of demyelination in the spinal cord, similar to those seen in subacute combined degeneration. (R. M. S.)

Diverticula of Lateral Ventricles.—A case is reported in detail and similar cases are described to illustrate that in rare instances protrusions, or diverticula, of the lateral ventricles may develop and extend into the cerebellar fossa near the apex of the tentorium.

It is suggested that these diverticula are the result of long-continued high intracranial pressure, with resultant internal hydrocephalus, and the development of a weak point in the floor of the lateral ventricles overlying the incisura tentorii. Any large space occupying lesion in the cerebellar fossa tends to keep the infratentorial pressure high and prevent the formation of such diverticula.

With the aid of ventriculograms these diverticula should be diagnosed with a fair degree of certainty when one is aware of their occurrence; otherwise they may be confused with a posterior protrusion of an enlarged third ventricle, a displaced fourth ventricle, or other abnormalities in this region. (R. M. S.)

Intracranial Blood Flow in Dementia Paralytica.—The authors' studies suggest that the total intracranial blood flow is diminished in persons who have a pathological diminution in brain volume, but that the blood flow per unit of brain substance may well be normal. Demented general paralytics and patients with marked cortical atrophy of the nonsyphilitic type showed most variation from the controls. (R. M. S.)

Factor of Hypoxia in Shock Therapies.—Patients with schizophrenia receiving various forms of shock therapy were studied. It was found that the oxygen saturation of the arterial blood diminished with the metrazol treatment when the convulsions were modified by administration of erythroidine or curare. Electrical shock therapy also revealed depression of the oxygen supply to the brain. A comparison was made between these physiological results and those obtained with other therapeutic agents: (a) metrazol alone; (b) potassium cyanide; and (c) insulin. With all these hypoxia occurred, with consequent depression of brain metabolism. The relation of this depression to the ameliorative effect on the course of the disease is discussed. (R. M. S.)

Parapyramidal Fasciculotomy in Brain Stem.—Siris reports a case of postencephalitis parkinsonism in which an incision into the region of the reticular formation in the medulla was made in the hope of interrupting parapyramidal pathways at a level more cephalic than is obtained by chordotomy. Relief was only transitory. Impairment of pain and temperature sensation in the contralateral lower limb was secured. Trigeminal sensation was undisturbed. The possibilities for further investigation of this problem are discussed. (R. M. S.)

Studies of Vibration.—Vibration sensibility was studied in the faces of nine patients who had been subjected to unilateral retrogasserian neurectomy. Thresholds of vibration sensibility at frequences of 100 double vibrations per second were ascertained for five different points on each side of the face and tongue, and the upper limit of frequency of vibration perceived was determined at these points under the limitation imposed by our apparatus. It was found that the loss of tactile sensibility and the preservation of pressure sensibility in the face are associated with diminution in vibratory sensibility in the lips and tongue. On the forehead and cheek vibration delivered by the apparatus under the conditions of the present experiment could not be perceived in most instances. It is suggested that the perception of vibratory stimuli in the face depends on the stimulation of both touch and deep pressure receptors. Vibration sensibility therefore is to be regarded as the perception of repetitive mechanical stimuli delivered either to deep or to superficial receptors or to both varieties. The type of apparatus used, the manner in which it is used, and the innervation of areas stimulated determine the relative importance of pressure on tactile end organs in the perception of vibration. (R. M. S.)

E. E. G's. of Thiamine-deficient Pigeons.—It is suggested that the changes in brain potentials in thiamine-deficient pigeons indicate marked facilitation of cortical discharge during the initial phases of thiamine deficiency, before its final depression. This type of effect is compared to that of oxygen and dextrose deficiency, in which similar changes in brain potentials occur. (R. M. S.)

Periarteritis Nodosa.—A case of periarteritis nodosa with predominantly neurological manifestations is reported. It is emphasized, from a review of the literature, that involvement of the central nervous system in this disorder is not uncommon. Pathogenetically, the condition is regarded as panarteritis and the parenchymal changes as of vascular origin. (R. M. S.)

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*Regulation of Cerebral Carbon Dioxide. E. F. Gibbs, F. A. Gibbs, W. G. Lennox, and L. F. Nims. 879.
Epidermoid, Dermoid and Teratomatous Tumors of the Central Nervous System. W. T. Peyton and A. B. Baker. 890.
*Pathologic Changes in the Central Nervous System in Experimental Electric Shock. G. Heilbrunn and A. Weil. 918.
*An Encephalographic Ratio for Estimating Ventricular Enlargement and Cerebral Atrophy. W. A. Evans. 931.
Fatal Infectious Polyneuritis in Childhood: Infectious Neuronitis, Acute Polyneuritis with Facial Diplegia, Guillain-Barré Syndrome and Landry's Paralysis. C. D. Aring and A. B. Sabin. 938.
*Familial Mental Deficiency Akin to Amaurotic Idiocy and Gargoylism: An Apparently New Type. G. A. Jervis. 943.
*Alternating Tremor and Its Relation to Cortical Pathways. B. H. Balser.
*Studies of the Corpus Callosum: III. A Contribution to the Study of Dyspraxia and Apraxia Following Partial and Complete Section of the Corpus Callosum. A. J. Akelaitis, W. A. Risteen, R. Y. Herren, and W. P. Van Wagenen. 971.
Disturbances in Brain Function Following Convulsive Shock Therapy: Electroencephalographic and Clinical Studies. N. A. Levy, H. M. Serota, and R. R. Grinker. 1,009.
Special Articles:
Clinical Notes from A Trip to Great Britain. W. Penfield. 1,030.

Regulation of Cerebral CO_2.—The response to over-ventilation and to breathing an increased concentration of carbon dioxide was studied in thirteen subjects with normal electroencephalograms and no clinical evidence of cerebral disorder. Two of the subjects were chosen because they showed an unusually rapid increase in amplitude and decrease in frequency of cortical potentials with over-ventilation. Simultaneous samples of blood were taken from the femoral artery and the internal jugular vein, and the values obtained for carbon dioxide content, *p*H, carbon dioxide tension and oxygen saturation were compared and correlated with simultaneously obtained samples of the electroencephalogram. The dilatation or constriction of cerebral arterioles which follows an increase or decrease of carbon dioxide in the arterial blood serves to protect the brain against undue shifts in carbon dioxide tension. The slow waves that appear in the electroencephalogram with over-ventilation are caused by a drop in cerebral carbon dioxide, and not by anoxia secondary to cerebral vasoconstriction. The ease with which such slow waves can be produced with over-ventilation is a rough index of the relative incompetence of the cerebral vasoconstrictor response to low carbon dioxide tension.

In some supposedly healthy adults and in most persons with petitmal epilepsy, the cerebral vasoconstrictor response to low carbon dioxide tension is defective, this defect resulting in abnormal slowing of the electrical activity of the cortex during over-ventilation.

The cerebral vasoconstrictor response to low carbon dioxide tension disappears when a critically low level of oxygen tension is reached. (R. M. S.)

Pathological Changes in C. N. S. in Experimental Electric Shock.—Rabbits and rats were subjected to electric shock treatment simulating the treatment of patients with "functional psychoses." Hæmorrhages were present within the meninges of the brain and spinal cord and within the brain stem and the spinal cord. These hæmorrhages were usually confined to the immediate neighbourhood of capillaries and small veins and were produced by the rupture of the walls of these vessels. A combination of causes was responsible for these ruptures: the sudden rise of the arterial blood pressure during the forceful contraction of the musculature, the vasospasm of the peripheral arteries following cessation of the electric stimulation and the stasis in the venous system, which was aggravated by cessation of respiration for several seconds. No generalized ganglion cell disease or generalized proliferative glial reaction was observed. Such phenomena were confined to the immediate proximity of the hæmorrhages and were usually combined with a somewhat farther-reaching edema of the surrounding tissues. (R. M. S.)

Encephalographic Ratio for Estimating Ventricular Enlargement.—The ratio of the transverse diameter of the anterior horns to the internal diameter of the skull as measured on encephalograms (or ventriculograms) exposed in the anteroposterior projection with the posterior part of the head down is proposed as an index of the size of the cerebral ventricles. The average value of the ratio for a "normal" group was found to be 0·23, with extreme values of 0·16 and 0·29. There is a significant correlation between the size of the ventricles and the size of the skull, and the ratio has the same average value for small and large skulls and for the skulls of infants, children, and adults. The great majority of normal values fall between 0·20 and 0·25; values above 0·30 indicate definite ventricular enlargement and provide a quantitative estimation of the degree of cerebral atrophy. Serial studies may give an indication of the course of the brain lesion and a basis for prognosis. (R. M. S.)

Familial Mental Deficiency.—Six cases of an apparently new type of familial mental deficiency are described. The clinical features consist of severe idiocy, stunted growth, characteristic facies and peculiar changes in the bones of the skull. Pathologically, there is ubiquitous swelling of the nerve cells with cytoplasmic infiltration of lipoid granules. The relation of this condition to juvenile amaurotic idiocy and gargoylism is discussed. Differences are indicated which appear to justify a separation of this type of mental deficiency. It is pointed out, however, that amaurotic idiocy, gargoylism, and the condition in the cases here reported show obvious similarities which warrant their inclusion in the same group of diseases. The pathogenesis of this condition is discussed, the morbid process being considered an instance of localized lipidosis. From the etiological aspect, the disease is considered to be genetically determined and, probably, inherited as a recessive. (R. M. S.)

Alternating Tremor.—A case is reported of bilateral paralysis agitans which had been present for twelve years when thrombosis of the right middle cerebral artery developed, with resulting left spastic hemiplegia, from which the patient recovers during the next three years with about 60 per cent. of voluntary motor power. The tremor (of paralysis agitans) never returned to the affected extremities, however. The rigidity, previously present, was not altered. Post-mortem examination revealed complete destruction of the head of the caudate nucleus, the putamen, part of the globus pallidus, and portions of the internal capsule. Three-fifths of the pyramidal tract, the whole frontopontile system and a part of the temporopontile system, the frontothalamic fibres to the anterior lateral thalamic nucleus, the corticorubral and the corticonigral fibres were affected. (R. M. S.)

Studies on Corpus Callosum.—In 18 cases of epilepsy the corpus callosum was sectioned in variable degrees. The extent of the division varied from merely section of the body and the posterior half of the genu to complete section of the corpus callosum. On the basis of this study the conclusion may be drawn that dyspraxia in the subordinate or dominant hand after partial or complete section of the corpus callosum occurs only when damage to the subordinate or dominant hemisphere coexists. (R. M. S.)

BRAIN

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Studies in Human Vestibular Function: II. Observations on the Directional Preponderance of Caloric Nystagmus ("Nystagmusbereitschaft") Resulting from Unilateral Labyrinthectomy. T. E. Cawthorne, G. Fitzgerald, and C. S. Hallpike. 138.
Studies in Human Vestibular Function: III. Observations on the Clinical Features of "Menières" Disease: With Especial Reference to the Results of the Caloric Tests. T. E. Cawthorne, G. Fitzgerald, and C. S. Hallpike. 161.
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Primary Degeneration of the Spinal Cord in Monkeys, a Study in Comparative Pathology. A. E. Hamerton. 193.
Aphasia in Children. E. Guttman. 205.
Cerebello-Olivary Degeneration: An Example of Heredo-Familial Incidence. F. Parkes Weber and J. G. Greenfield. 220.

Chronic Thyrotoxic Myopathy.—Three new cases are described and ten published cases summarized. Two of the personal cases recovered following thyroidectomy, one died undiagnosed. The condition is one of generalized atrophy of voluntary muscle, with coarse fasciculation. It may be asymmetrical, and is shown to be due to a peripheral lesion of muscle. The hyperthyroid symptoms are not marked, but the B.M.R. is always moderately raised. This is not due to the severe fasciculation. Thyroidectomy is followed by complete recovery. A myasthenic response is obtained from the affected muscles, but muscles innervated by cranial nerves are not involved. (D. J. W.)

Spinal Cord Degeneration in Monkeys.—Eleven cases of the demyelinating disease of the spinal cord in monkeys described by Sherer in 1932, have occurred in the London Zoo in the last seven years. They were all in old-world monkeys, African and Asiatic. Pathologically the disease is indistinguishable from subacute combined degeneration of the cord and in three cases in which gastric analysis was performed there was achlorhydria. Macrocytic anaemia was found in one. It is not yet claimed that this disease is identical with subacute combined degeneration of the cord. (D. J. W.)

Aphasia in Children.—Aphasia occurred with the same regularity in thirty cases of cerebral hemisphere lesions in children as in adults. The picture is predominantly one of diminished speech production, purely motor aphasia recovering very rapidly, those with a reversible lesion recovering within four weeks. Little impairment in intelligence was found although right-sided lesions without aphasia showed retardation. This suggests that the brain damage rather than the aphasia is responsible for intellectual deterioration when it is present. (D. J. W.)

Cerebello-Olivary Degeneration.—A case is described of progressive ataxia due to parenchyatous degeneration of the cerebellum causing disappearance of the Purkinje cells with degeneration of the inferior olivary nucleus. Similar symptoms were present in the female patient's

mother and daughters. The cerebellar degeneration was most marked in the superior surface of the cerebellum, It is considered that the degeneration of the inferior olives is secondary to this. The case is therefore quite distinct from olivo-ponto-cerebellar atrophy where the olivary degeneration is primary. (D. J. W.)

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Effects evoked in an Axon by the Electric Activity of a Contiguous One. A. Arvanitaki. 89.

Localization of Enzymes in Nerves. I. Succinic Dehydrogenase and Vitamin B_1. D. Nachmansohn and H. B. Steinbach. 109.

Cerebellar Action Potentials in Response to Stimulation of the Cerebral Cortex in Monkeys and Cats. Robert S. Dow. 121.

The Effects of Polarization on Nerve Action Potentials. Helen Tredway Graham. 137.

Stimulation of Peripheral Nerve Terminations by Active Muscle. David P. C. Lloyd. 153.

Contiguous Electric Activity in an Axon.—Stimulation of axons in contact (ephapse) by interaction has been studied in Sepia. Current spread from the active axon serves as a polyphasic electrical stimulus to the contiguous axon. When the contact conditions allow of a large final positive phase in the resting axon they produce no visible effect on it; when the negative phase predominates active electrical reactions arise. Spikes occur 2 to 5 m/sec after the afferent spike reaches the contact zone. Subthreshold afferent spikes will augment spontaneous oscillations of the efferent axon and in time produce a spike. The relation of these results to synchronization of central cell bodies is discussed. (W. M. H.)

Localization of Enzymes in Nerves.—In the giant fibres of the squid most of the succinic dehydrogenase is found in the axoplasm. Diphosphothiamin is concentrated several times, more in the sheath than in the axoplasm. This fact supports the assumption that Vitamin B_1 is required for the formation of acetic acid for acetylcholine from pyruvic acid. The distribution differs from that of choline esterase as well as from that of succinic dehydrogenase. (W. M. H.)

Cerebellar Action Potentials and Stimulation of Cerebral Cortex.—Oscillographic study has been made of responses in the cerebellum of the cat and monkey to single shock electrical stimulation of the cerebral cortex. The growth of cortico-ponto-cerebellar connections in the monkey appears to be in some degree at the expense of spinocerebellar connections. In the monkey the most widespread cerebellar potentials arose from stimulation of areas 4 and 6 and the postcentral gyrus. There was a tendency for the face area to show most low threshold responses in the more rostral lobes while the leg zone was more heavily represented in the caudal lobules. The arm area was intermediate. No differences between topographical areas could be detected if only the presence or absence of response was observed. (W. M. H.)

Polarization and Nerve Action Potentials.—In A fibres of amphibian and mammalian nerves spikes and negative after-potentials are increased in amplitude at the anode and decreased at the cathode; positive after-potentials are modified by polarization in the same way as the negative potentials they succeed. Study of conditioned responses shows a more rapid recovery and greater tendency to supernormality with anodal polarization, slower recovery and suppression of supernormality with cathodal polarization. Thus polarization, while modifying after potential, does not alter the relationship of after potential to recovery. In C fibres the changes in amplitude are comparable with those in A fibres but the after potential changes are relatively greater. If the slower components of the action potential be included the increment-decrement law becomes an adequate formulation of the facts. (W. M. H.)

Stimulation of Peripheral Nerve Terminations by Active Muscle.—Secondary centripetal discharges are found in the ventral root and neighbouring ventral and dorsal roots when a muscle is activated indirectly by a motor nerve volley. The latency of the discharge is equal to the sum of the conduction time of nerves to and from the muscle, neuro-muscular delay and a short utilization period. The time of origin of the discharges corresponds approximately to the period of the ascending phase of the muscle action potential at or near the junctional region. Secondary centripetal discharges follow exactly the stimulus frequency at frequencies yielding mechanical fusion of muscle contraction. Muscle contraction as responsible for their initiation is therefore excluded. (W. M. H.)

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*The Compensatory Mechanism of the Splanchnic Circulation during Changes of Posture. O. G. Edholm. 1.

The Effect of Partial Pancreatectomy on the Concentration of Insulin in the Pancreatic Remnant. H. J. Bell, C. H. Best, and R. E. Haist. 11.

The Effect of Insulin and Anterior Pituitary Extract on the Insulin Content of the Pancreas and the Histology of the Islets. C. H. Best, J. Campbell, R. E. Haist, and A. W. Ham. 17.

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Diffusion Relations of Urea, Inulin and Chloride in some Mammalian Tissues. E. J. Conway and O. Fitzgerald. 86.

*The Effect of Hypertonic Glucose Solutions on the Inflow of Normal Saline Solution into the Sub-Arachnoid Space of a Dog. 106.

A Method of Conducting a Biological Assay on a Preparation giving Repeated Graded Responses Illustrated by the Estimation of Histamine. 115.

The Effect of Sodium and Calcium on the Toxicity of Potassium in Mice. C. W. Emmens and H. P. Marks. 131.

Compensatory Mechanism of Splanchnic Circulation.—In the cat fall of blood pressure in the feet-down position is due to collection of blood in the liver. Evisceration fails to abolish the fall but diminishes the vascular compensation after the fall; removal of the liver both after evisceration and independently almost abolishes the fall. Recovery of blood pressure on return to the horizontal is due to the return of blood, accumulated in the liver, to the right side of the heart. (W. M. H.)

Hypertonic Glucose Solutions and Inflow of Normal Saline Solution into Subarachnoid Space.—Contrary to the findings of others in cats is this report of increased c-s-f pressure, increased brain volume, and diminished rate of inflow of normal saline solution into the subarachnoid space of the dog on intravenous injection of hypertonic glucose solutions (50 and 25 per cent.) in dogs. The rapid production of cerebral œdema is the most characteristic effect of hypertonic glucose and lævulose solutions. Hypertonic sodium chloride (25 per cent.) has a similar action, but the onset of œdema is not so rapid. (W. M. H.)

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BOOK REVIEWS

THE HUMAN MIND. THE ORGAN OF THOUGHT IN FUNCTION AND DYSFUNCTION

Mudro Mackenzie, M.D., M.R.C.P.

(J. and A. Churchill, Ltd., London. 1941)

The themes running through Dr. Mackenzie's attempt to describe the workings of the mind as a discrete organ are anxiety, depression, apathy; simplification and amplification; deliberation and immediacy. By writing these words with a capital letter he gives them a more technical appearance and meaning than most of them usually bear: thus the last two pairs just mentioned are described as contrasted forces driving the mind. The exposition is mostly on this level, and will not attract the reader with scientific training: it is too like a nominalist's caricature of realist doctrine.

ENCEPHALOGRAPHY

E. Graeme Robertson

(Macmillan & Co., Melbourne. . Pp. 105. 32*s*. 6*d*.)

(Monograph from the Walter and Eliza Hall Institute of Research, Melbourne)

Dr. Robertson's monograph will be welcome both to neurologists and to neuro-radiologists.

Encephalography has suffered in this country from inadequately controlled technique and often from lack of co-operation between clinician and a full-time radiologist. The technique described in this book is a refinement of the lumbar route, but the subject is discussed in a well-balanced manner and the indications for and use of the cisternal route are by no means ignored. It must be realized that so thorough a technique will be time-consuming and that encephalography, to get the best results, must be regarded less lightly than has at times been the case in the past, when a standard series of views after a routine filling, without radiographic control, has been the rule.

An excellent anatomical study of the filling of the various parts of the sub-arachnoid spaces, the cisterns and the ventricles is made, and abnormal conditions are well illustrated clinically by case notes. The only point which is not made quite clear is the influence of purely radiographic factors on ventricular measurements, for the assessment of which knowledge of the apparatus and technique is essential.

The make-up of the book is good and the illustrations and reproductions of X-ray films are really first-class. It can be confidently recommended as a concise and comprehensive review of the subject and should do much to keep encephalography in its proper perspective in neurological investigation.

THE NEUROSES IN WAR

Several Authors under the Editorship of Emanuel Miller

(Macmillan and Co., Limited, London. 1940. Pp. 240. 10*s*. 6*d*.)

So much has been written on neuroses, and especially on the neuroses of war, that a compendium cannot be expected to say anything new: much of the book might have been written in 1919. A series of opinions and recollections such as this is, however, valuable if it sifts the inchoate material deposited in medical journals and doctors' memories, keeping only what a riper judgment and experience can approve. Thus there is a useful chapter reviewing briefly the literature of the subject, on much the same lines as earlier compilers. The bulk of the book deals with the psychopathology and clinical forms of diagnosis and treatment of neuroses in soldiers: there is also an essay on civilian reaction, morale, and prophylaxis which is original and informative though at many points the subsequent events have shown how difficult it is to apply some doctines of psychological medicine to the solution of social problems, actual or imminent.

ANXIETY AND ITS TREATMENT

John Yerbury Dent

(John Murray, London. 1941. Pp. 124. 3*s*. 6*d*.)

Written in simple language for the lay public, this is a discursive treatise on alcohol and its effects, with some general psychiatry and physiology to make good measure. Much of it is correct, or only slightly distorted, but there are some bad descriptions (as of the Korsakow syndrome) and misleading comparisons, e.g. between diabetes mellitus and addiction to alcohol: " we are not born alcoholic or diabetic but we can with persistent poisoning by alcohol or sugar become alcoholics or diabetics. In alcoholism there is inefficiency of the liver, in diabetes of the pancreas . . ." and so on. A detailed account of the apomorphine method of treatment, with which the writer had had much experience and success, is given, and a final chapter gives commonsense advice about how people should behave during air raids.

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